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THE STATISTICAL METHOD

A VITAL TOOL IN CLINICAL MEDICINE

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CLINICIANS seem to have an innate fear of mathematics. Hence, the statistical method, which could serve them as a valuable tool, is now used for the most part by the research workers and the academic laboratories. Medical journals contain an increasing number of papers based upon mortality and morbidity rates on groups of patients who have received different treatments. The conclusions of most of these papers based upon rates and percentages are worthless.

A statistical analysis of percentages would do much to clarify the present muddled state of the profession regarding the correct treatment of many common maladies. It is common at medical meetings to observe doctors presenting figures showing that a certain procedure in the hands of one has been attended by a decreased mortality; in the hands of the other, by a heightened mortality. Each implies that the other is a prejudiced observer (or worse); each maintains that the percentages derived from his series are conclusive. More often than not, each protagonist bases his contention on mere chance variation; had either or both been aware of the rudiments of the statistical approach, there would have been no controversy.

The following, although hypothetical, is typical of statements in clinical literature: "In the series with delayed operation the mortality was 1.5 per cent, whereas in the series with immediate operation the mortality was 4.8 per cent. Thus it is seen that death occurs more than three times as frequently after immediate operation." It is true that 4.8 is more than three times 1.5; however, from the standpoint of recovery there is little difference between 95.2 per cent and 98.5 per cent. Any two therapeutic procedures which result in recovery so frequently cannot be very different. The differences between 1.5 and 4.8 per cent and

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between 95.2 and 98.5 per cent are the same. The important fact is that the difference is 3.3 per cent, not that 4.8 is three times more than 1.5 per cent.

In recent years increased emphasis upon good hospital records is making a large mass of data available to the profession. At every medical meeting and in every medical journal doctors are constantly trying to draw sound conclusions from these figures. With few exceptions, they do not know how. The profession has failed to equip itself with the knowledge necessary to find the truth buried in its own records.

There is a simple method by which percentages may be analyzed, based upon two factors inherent in every percentage. We shall later consider the derivation of the method, but now we give the rule of thumb by which the doctor may compute the soundness of the conclusions upon the margin of the paper in question. The following is the formula for the "standard error" of the difference between two percentages.

$$\sqrt{\frac{\text{Percentage A} \times (100-\text{Percentage A})}{\text{No. of cases in Series A}} \text{ plus } \frac{\text{Percentage B} \times (100-\text{Percentage B})}{\text{No. of cases in Series B}}}$$

If the difference between Percentages A and B is less than twice the figure resulting from the above formula, the difference is not statistically significant and may be considered as due merely to chance.

The steps by which this formula is derived and its practical application may now be described briefly.

There are two factors that govern the reliability of any percentage. First, the reliability of a percentage varies with the length of the series. It may be said to be intuitively obvious that 4 per cent of 1,000 is more reliable than 4 per cent of 50. As a first step in the derivation of our formula we may say that:

$$\text{Reliability increases with length of series,}$$
$$\text{or}$$
$$\text{Unreliability (error) decreases with } \frac{1}{\text{length of series.}}$$

This is another way of saying that the error will be smaller as the length of the series or number of cases (n) is larger.

Second, the man in the street realizes that any percentage in the neighborhood of 50 (50-50) is less reliable than a percentage nearer the extremes of 0 or 100. It is an interesting and useful fact that $50 \times 50 = 2{,}500$ and $1 \times 99 = 99$. If one multiplies any percentage by its complement, one gets a figure that is larger as one approaches "fifty-fifty."

$$\begin{aligned} 10 \times 90 &= 900 \\ 20 \times 80 &= 1{,}600 \\ 30 \times 70 &= 2{,}100 \\ 40 \times 60 &= 2{,}400 \\ 50 \times 50 &= 2{,}500 \end{aligned}$$

Thus we may say,

$$\text{Error varies with percentage} \times (100\text{–percentage}).$$

Then if we combine these two notions of error, we find, with corrections, that

$$\text{Error varies with } \frac{\text{Percentage} \times (100\text{–Percentage})}{\text{n}}$$

It can be proved that the error varies as the square root of these factors. If a series becomes ten times as long, the error is not decimated but is decreased only to $\frac{1}{\sqrt{10}}$ of its previous value. Hence the formula becomes for a given Percentage A,

$$\text{Standard Error (S.E.)} = \sqrt{\frac{\text{Percentage A} \times (100\text{–Percentage A})}{\text{No. of cases in the series}}}$$

$$= \sqrt{\frac{\text{A} \times (100\text{–A})}{\text{n}}}$$

We are now in a position to consider critically the hypothetical statement regarding the merits of early and delayed operation. It is seen that the length of the series is completely ignored. The raw percentages, unmodified by length of series, are used to draw a sweeping conclusion. The other factor, the size of the percentages, is likewise ignored. For convenience in computation let us assume that each percentage was based upon a series of 100 operations. Then in the case of delayed operation

$$\text{S.E.} = \sqrt{\frac{1.5 \times (100 - 1.5)}{100}} = \sqrt{\frac{1.5 \times 98.5}{100}} = \sqrt{\frac{147.75}{100}} = \sqrt{1.4775} = 1.21,$$

and in the case of immediate operation

$$\text{S.E.} = \sqrt{\frac{4.8 \times (100 - 4.8)}{100}} = \sqrt{\frac{4.8 \times 95.2}{100}} = \sqrt{\frac{456.96}{100}} = \sqrt{4.5696} = 2.13.$$

The respective mortalities, then, are not merely 1.5 and 4.8 per cent, but 1.5 ± 1.21, and 4.8 ± 2.13 per cent. Thus, in another identical series the chance (derived by a mathematical process we need not consider here, but which may be obtained from any book on statistics) is 1 in 3 that either of the mortality percentages might vary as much as one standard error and 1 in 22 that either might vary as much as twice its standard error. In other words, in another completely similar group of patients, there is a possibility that the mortality percentages might be exactly equal, 2.7 for delayed operation, i.e., $1.5 + 1.2$, and 2.7 for immediate operation, i.e., $4.8 - 2.1$.

Thus far we have considered the individual percentages and their standard errors; but, if percentages may vary so much, the difference between them will vary likewise. The difference between two percentages has its own standard error derived from the standard errors of the

percentages themselves. The standard error of the difference between Percentages A and B equals the square root of the sum of the squares of the two standard errors.

$$\text{S.E. diff.} = \sqrt{\text{S.E.}_{A}^{2} + \text{S.E.}_{B}^{2}} \quad .$$

In our series the difference is 3.3 per cent, and S.E. diff. =

$$\sqrt{1.21^{2} + 2.113^{2}} = \sqrt{1.4775 + 4.5696} = \sqrt{6.0471} = 2.5.$$

The difference actually is 3.3 ± 2.5 per cent.

Statisticians vary as to what is a "significant" difference; i.e., a difference sufficiently great to be due to causes other than chance. The minimum requirement is a difference at least twice its standard error. In other words, the odds must be at least 21 to 1 that the difference did not occur by chance. Some are better satisfied if the difference is three times its standard error. Others compromise on a difference which is 2.5 times its standard error. It depends upon the individual's concept of "certainty." If a difference between percentages is twice its standard error, the odds are 1 to 21 that a difference as large as this could occur simply by chance. To some workers this is "certainty." If the quotient obtained by dividing the difference by its standard error is 2.5, the odds are 1 to 80 and, if the quotient is 3.0, they are 1 to 369. One may take one's choice, but, when the quotient is less than 2, the reality of the difference can be established only by amassing a larger series of cases.

In our hypothetical series the difference is less than twice its standard error. The quotient obtained by dividing the difference by its standard error, 3.3 ÷ 2.5, is 1.3. Therefore, while the delayed operation may be better, that conclusion is not justified when based on this series. Further study must be made or this series must be combined with similar series from other hospitals. And it is quite possible that the proportions in another hospital would be exactly reversed.

Yet the mortality of immediate operation, in the hypothetical series, was "more than three times the mortality of delayed operation." This type of conclusion which sounds so important is gravely misleading, because it ignores the basic rules for evaluating data accumulated from a small sample in terms of its probable occurrence in the unselected population.

To compute the standard errors of percentages is a simple and absolutely necessary procedure. For example, there recently appeared in an American surgical journal an article in which an internationally known surgeon argued strongly for early operation in acute cholecystitis. His conclusions were based on a series of 97 late operations with 7.2 per cent mortality and 62 early operations with 3.2 per cent mortality. The difference between these percentages is 4.0 with a standard error in this

series of 3.4. Obviously this result has no statistical significance because the quotient (4.0 ÷ 3.4) is only 1.2, far below the minimum of 2.0, and represents odds of only 3 to 1 that the difference did not occur by chance alone. A few months later two prominent American surgeons reported a series of 144 early operations (within seventy-two hours) with a mortality rate of 7.6 per cent and 176 late operations with a mortality rate of 3.4 per cent and concluded that late operation was better. The difference in this series is 4.2 ± 2.6 per cent; the quotient (4.2 ÷ 2.6) is 1.6 and hence the difference cannot be considered as beyond the range of chance variation. Both protagonists are drawing conclusions which are not justified by the series at hand.

Thus far we have considered the application of statistical method to percentages only. Although the percentage, e.g., morbidity or mortality rate, is the device most used by clinicians to draw comparisons in scientific papers, the arithmetic mean, the average, is also frequently used. What has been said of the importance of the statistical method in relation to percentages applies with equal force to the average.

It is obvious that: (1) an average derived from a large number of closely grouped observations is reliable; (2) one derived from a small number of widely dispersed observations is unreliable. The reliability of averages may be reduced to a numerical measurement much the same as in percentages. The "standard deviation" becomes the numerator of our fraction and the square root of the number of cases remains the denominator. I suggest that the reader consult Fortuyn or Hill as to the manner of computation of the standard deviation.

I have tried to emphasize the great importance of statistical method, but this does not constitute the whole picture. Accurate observation and logical reasoning are as important as they ever were. They are even more important, if possible, because, to borrow a chemical phrase, the end point has been so sharpened by the statistical method that errors in observation and reasoning are magnified. Clinical investigation may be said to have passed from the qualitative to the quantitative stage with all the painstaking accuracy that this step implies. The statistical method is not a smoke screen for slovenly work. It will not make answers right if the basic reasoning is wrong. It will not correct errors in observation for it can be applied only after the data are collected. The statistical method is but an extension of reasoning.

An example of failure in this respect is the long-standing controversy concerning early *versus* late operation in acute cholecystitis. Many authors of medical papers attempt to ascertain the effect of one variable while ignoring the presence of another. In the literature on cholecystitis an author may classify a patient who enters the hospital on the fifth day of the disease and has an operation within twenty-four hours as an early operation and the patient who enters within twenty-four hours of the onset and has the operation three days later as a late opera-

tion. It is not surprising that ambiguous conclusions emerge. The only logical method is to divide the cases into three groups: those entering the hospital within twenty-four hours of the onset, those between twenty-four and seventy-two hours of the onset, and those entering after seventy-two hours. Then in each group the effects of early and late operation can be determined.

This necessitates a total series of about 1,000 patients, which is too much to expect of the clinicians today. As it is now, the individual series are too short for sound conclusions and the series of various authors cannot be combined because the methods of tabulation differ. It would be profitable if some authoritative surgical association erected a few rules under which gall bladder and other statistics were assembled. Then by a combination of series, reliable conclusions might be attained. As an example we suggest the following outline for assembling statistics on cholecystitis:

A. Home treatment, 0-23 hours
   1. Operated upon in first 24 hours at hospital
   2. Operated upon in second 24 hours at hospital
   3. Operated upon in third 24 hours at hospital
   4. Operated upon in fourth 24 hours at hospital
   5. Operated upon in fifth 24 hours at hospital or thereafter

B. Home treatment, 24-47 hours
   Same as under A

C. Home treatment, 48-71 hours
   Same as under A

D. Home treatment, 72-95 hours
   Same as under A

E. Home treatment, 96 hours or more
   Same as under A

This may seem at first to be unnecessarily complex, but a moment's reflection will reveal that it is what every clinician would like to do; but, when he assembles his cases, he finds that he does not have sufficient cases to make the population of any one group large enough and so makes his classification coarser.

Thus far the age factor has been completely ignored. The above classifications should be repeated for each ten-year age group. No clear-cut teaching has yet emerged in the literature largely because the age factor has been universally ignored. To my knowledge, no report has yet appeared which yields statistically impeccable conclusions. But within five years of this date, a clear-cut answer to this problem could be made if twenty outstanding clinics would adopt a standard classification and submit their data to statistical analysis. This is only one of several problems confronting surgeons which require the statistical approach for their solution.

THE REMEDY

What are we to do about the statistical approach in medicine? The answer rests with the medical schools, which must train every student in the rudiments of the statistical method. Medical schools train students

in the experimental method, but they have thus far neglected to teach them an equally useful approach, the statistical method. Twenty years ago Kilgore saw the problem clearly and urged that statistical method have a place in the medical curriculum. There are signs that the medical schools at long last are about to offer courses in statistics to their students.

Pending that long-delayed day when every doctor shall be aware of the necessity of the statistical method in clinical medicine, much can be done by an enlightened medical editorship. Medical editors should demand that statistical papers be properly analyzed and should refuse publication when the standard deviation or standard error is not included. Medical editors must eliminate or educate uninformed authors and inculcate a statistical *critique* in the medical reader.

SUMMARY

1. Clinicians have almost entirely neglected criteria of statistical analysis in their scientific writings.

2. The many contradictory teachings and controversial practices originate in part in this neglect of well-recognized statistical procedure.

3. We have described in detail the derivation and application of the simpler formulas as they relate to percentages.

4. With a little thought every doctor can master this technique and apply it in a very few minutes to medical papers which utilize percentages in their conclusions.

5. As presented now, most case series are too brief for sound conclusions. Publication should be withheld until longer series are amassed.

6. A standard classification in such diseases as are now the center of controversy would enable short series to be combined and allow reliable conclusions to emerge.

7. Medical students should receive formal education in statistical procedure.

8. Medical editors should demand of medical authors that their figures and data be statistically sound.

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A BULLET IN THE HEART FOR TWENTY-THREE YEARS

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"Now, slowly, let us hear what befell afterwards—step by step omitting nothing." Kim.

A GENERAL interest in the fate of foreign bodies and recent publications dealing with their effect when lodged in or about the heart encourage me to report the case of a man who is alive and well and has gone about his daily work for the last twenty-three years with a machine-gun bullet lodged in the wall of the left ventricle.

The patient, an officer, 32 years of age, was admitted to a base hospital under my care in April, 1917. Eighteen days before admission, while in the open, he was struck on the front of the left side of the chest by a bullet from a machine gun at an estimated range of 500 yards. There was a snowstorm at the time, and, though he does not remember exactly what he was doing, he thinks he may have had his left arm held up in front as some protection against the driving snow. There was a through-and-through bullet wound of that arm just above the elbow, and he believes that may have been inflicted by the bullet which penetrated the chest. In its course the missile traversed a service waterproof and the left breast pocket of his tunic and its contents, consisting of a bundle of six letters and a pocketbook one-half inch thick (Fig. 1), at the same time grazing the edge of a wooden ruler and, of course, penetrating his shirt (Fig. 2.) He had no clear recollection of what happened immediately after the casualty but only a hazy memory of lying on a stretcher at a field ambulance where he had some tea. From there he was moved to a C. C. S. about twelve miles behind the line. Recollection of that hospital mostly concerned a pain which he felt in the left ear and which he attributed to an old otitis from which he had suffered since early youth, and which he thought had been lighted up by the journey on the stretcher with his head exposed. After three days he reached a base hospital in France from which he was transferred as a lying case to the First Northern General Hospital where he came under my care. When I first saw the patient, his only complaint was of some slight soreness about the situation of the wound on his chest. He lay still and quiet, but only because he had been told that he must take great care and insist on being carried. In general appearance he was a well-developed man with rather a big chest. He looked fit and well and made no complaint. At the onset I would like to say that this patient was of a calm and equitable temperament and with a sane outlook on life which throughout all the years I have known him has commanded my continued admiration and respect. Local examination disclosed a small wound of entrance one-half inch below and one-fourth inch external to the left nipple (Fig. 3), but there was no wound of exit. There were the scars of the through-and-through wound about two inches above the left elbow, but this had apparently done no damage and there was never any disability arising from it. The situation of the wound on the chest wall at once suggested the possibility of some cardiac injury, but there were no characteristic signs. The pulse was regular, steady, and of an average rate of 64 to the minute; the temperature was normal. There was no dyspnea, though, of course, the patient was kept quietly in bed. My colleague, Lieut.-Colonel Thomas Beattie examined the patient and reported as follows:

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"Slight deficient expansion on left side of chest. No impairment of percussion resonance. Breath sounds enfeebled vesicular over left base and axillary region but definitely audible and accompanied by some coarse crepitations. Vocal fremitus and vocal resonance present but diminished as compared with right side. Apex beat in fifth left interspace in nipple line. Heart action regular, no valvular defect, no pericardial friction."

An x-ray examination disclosed a service bullet with its base anchored probably near the tip of the left ventricle (Fig. 4). Not only was the foreign body pulsing with the regular heart beat, but its point was whirled about in the blood vortex in the heart cavity. Never before or since has it been my lot to witness a fluoroscopic examination which excited more vivid interest—a metallic foreign body which had

Fig. 1.

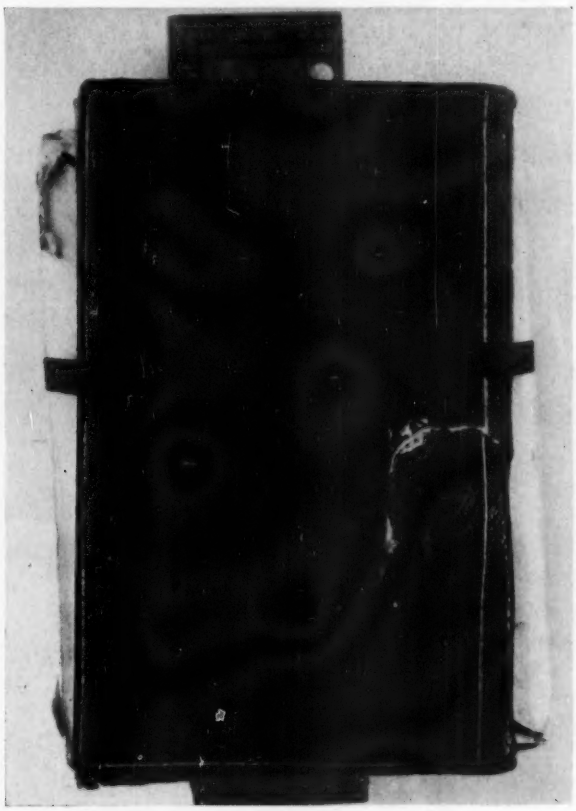

Fig. 2.

Fig. 1.—Contents of pocket traversed by bullet.
Fig. 2.—Notebook and scale perforated by bullet.

reached the heart cavity without killing the patient, and was merely anchored by its base to the heart wall, while its apex was whirling about in the blood stream like a weed growing from a stone at the bottom of a mill race. An electrocardiogram (Fig. 5*A*) was submitted to the late Sir James Mackenzie who kindly reported upon it as follows:

"The electrocardiogram shows nothing peculiar, excepting in the second lead where the wave T is inverted. This inversion of T was assumed at one time to be of serious significance, but I have watched cases who show it for a great many years, and this view has turned out to be unjustified. We do not know why T should be inverted. It is very well marked in your tracing. I shall be pleased if you will let me know how things transpire later."

While the excitement of our discovery continued, the patient was apparently quite well and was finding enforced rest very irksome. On May 12 he was allowed to get up and as there were no harmful effects we both became bolder and the patient was allowed to go to the toilet, to walk about the ward, and to walk with care up and down stairs. He was taking ordinary food and smoking cigarettes in moderation as was his wont.

Meanwhile the proper management of the case was giving me earnest consideration. The bullet, I concluded, was not completely embedded in the heart wall but merely tethered by its base, the apex being free in the cavity. A priori it seemed that the patient ran a great risk with a foreign body in so precarious a position and I was fearful lest at any time it would become dislodged and cause fatal

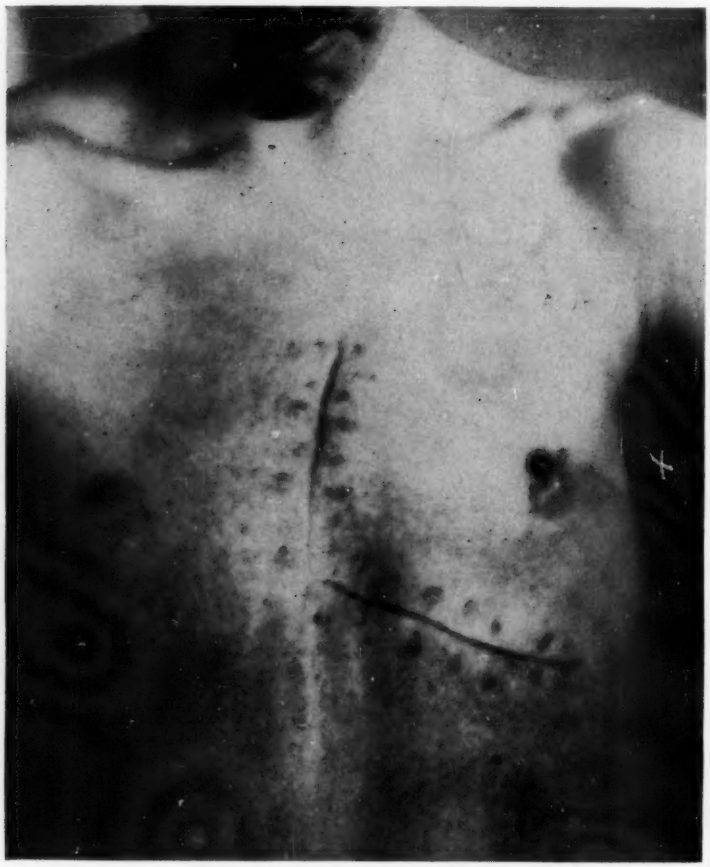

Fig. 3.—Scar of wound, showing entrance of bullet just below left nipple; also the incision employed for exposure of the heart.

embolism or that blood clotting about the foreign body would produce a thrombosis which might behave in the same way. On the other hand the risks of its removal one knew must be considerable, but some few surgeons like Beausseant (Bull. Acad. de méd., meeting of May 4, 1915) of the French Army and others had already been rewarded by success. After summing up the situation and discussing the matter with my colleague, Lieut.-Colonel Beattie, it was proposed to the patient that I should at least make an attempt at the removal of the unwelcome visitor and he willingly agreed. In my own mind I determined that discretion should be the better part of valor, but, nonetheless, I felt very confident in judicious intervention especially as I pictured the possibility of the base of the bullet being visible on the outer surface of the heart wall.

The operation was carried out on a never-to-be-forgotten Sunday morning, May 20, 1917, just thirty-nine days after the receipt of the casualty. Mr. W. E. M. Wardill and Mr. Rochester Smith acted as assistants, while Lieut.-Colonel Beattie and Major F. Pybus were also present. Captain H. H. Markham gave the anesthetic; induction was by A. C. E. followed by open ether, and this proved most satisfactory throughout. The approach was a left parasternal one and the general technique was as described by Kocher in the third English edition of his textbook, *Operative Surgery*.

Under the anesthetic it was noticed that the left chest did not expand as well as the right and that the intercostal spaces were drawn in a little. The skin incisions were as shown in the illustration (Fig. 3). As a first step the sixth costal cartilage was excised. There was no difficulty in carrying this out, and the pericardium was easily exposed by dividing the attachment of the triangularis sterni

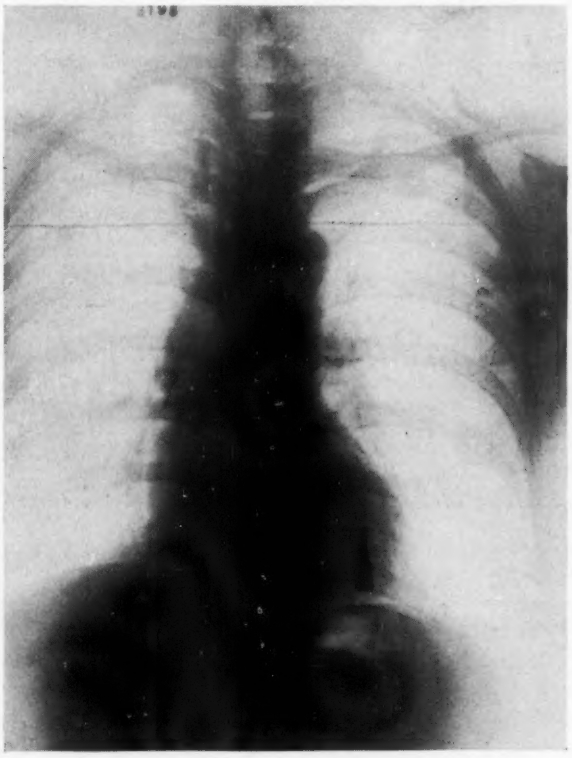

Fig. 4.—The bullet in the heart.

along the seventh costal cartilage and the end of the sternum and pushing it outward and upward together with a good deal of fat. As soon as this had been done, air began to be sucked into the cellular tissue around the pericardium, to such an extent that this area rapidly became emphysematous. It closely simulated air in the pleura and throughout the operation was rather an anxiety, though it was controlled to some extent by covering up the exposed part with large wet swabs of gauze. The fifth and fourth rib cartilages were next cleared, the pleura being separated from their deep surfaces and gently pushed outward by the finger before they were divided.

The flap of chest wall was then bent outward, but, as this did not give enough working space, the third cartilage was also cut through and displaced. During this latter step the internal mammary vein was torn and almost at once the area became obscured by frothy blood which might have been a great nuisance, but

fortunately the vessel was easily caught and tied. Up to this time the respiratory movements had been rather labored and noisy, but they became quieter before the pericardium was incised. The latter was not distended and was readily opened by an oblique incision about two inches long made in the direction of the sixth cartilage.

Some small amount of blood-stained fluid escaped, but there were no clots and no adhesions so that one could only conclude that there had scarcely been any bleeding into its cavity. The incision in the pericardium was next prolonged upward by the side of the sternum to the level of the upper border of the fourth cartilage and later to the third; there was no bleeding from its cut edge.

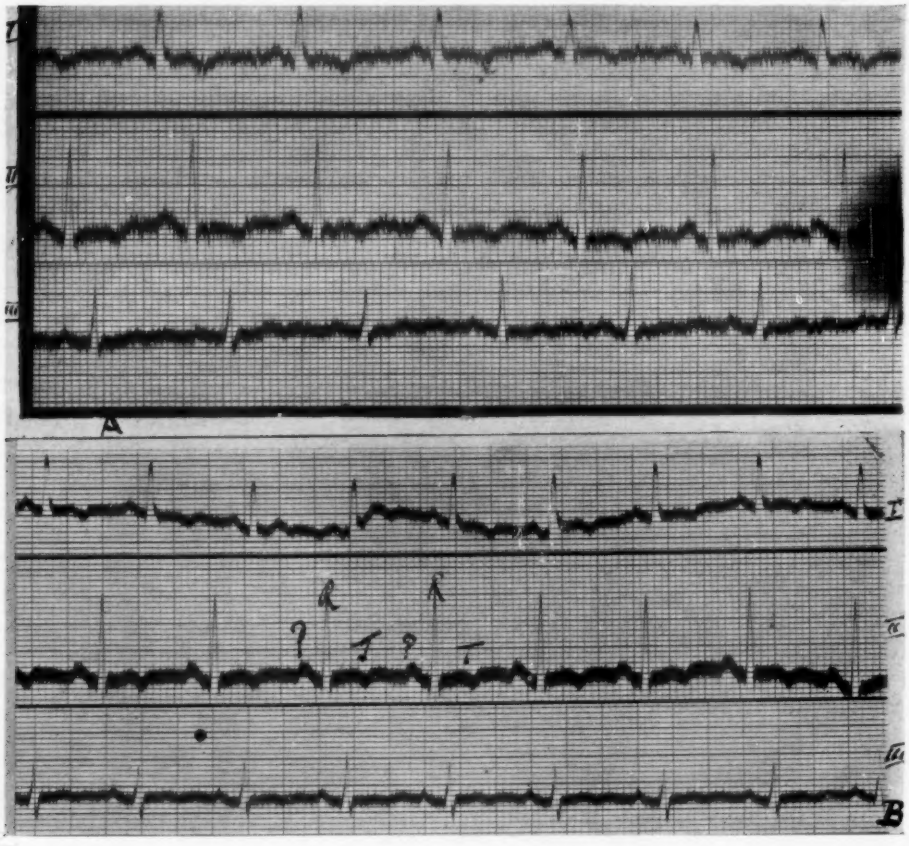

Fig. 5.—Electrocardiograms (limb lead) taken just before (*A*) and three months after (*B*) operation.

The heart, when first exposed, began to beat in a tremulous fashion, but this quickly ceased and throughout the subsequent manipulation its movements were very steady. Just after first administration of the anesthetic the pulse rate was 120 and of rather low tension, but at a later stage it was only 65 and of normal tension. At first sight of the naked heart nothing abnormal was noticed, but on further examination the spot where the bullet had entered was seen about the middle of the outer border of the left ventricle slightly toward its posterior aspect. It was a definite depression surrounded by a roughened whitish area on the visceral pericardium. Just opposite this point on the inner surface of the pericardial sac the scar of the wound of entrance was plainly seen. The heart muscle in the neighborhood of the wound felt firm, but I could not satisfy myself that the bullet was

lying there and palpation in the vicinity did not disclose its whereabouts. What was at first taken to be the bullet was felt to the right of the left coronary artery and at a spot near the junction of the auricle and ventricle, but the more this area was palpated the less did the hardness detected seem like a foreign body.

It must be remarked that the varying status of the heart muscle in systole and diastole made observations by palpation very difficult, for at the best diastole allowed only a second of relaxation, which is a very short time for accurate observation, and during systole the muscle became stony hard. After further negative palpation the region of the scar and the area near the ventricular base were explored by puncture with a straight needle but without striking anything metallic. The heart muscle was surprisingly tough and the punctures only bled momentarily. The region of the left auricle was then explored, but nothing abnormal could be detected.

It was still felt that the bullet might be lodged about the suspected area near the base of the ventricle. To steady the heart for final exploration a stitch of fine catgut was passed into the wall of the ventricle just by the side of the entrance scar. It was found difficult to manipulate a needle holder and in view of the possibility of having to open the heart and suture it rapidly a little more working space was felt to be necessary. This was secured by cutting away the sternal remains of the divided costal cartilages with rongeur forceps. This was a considerable help, but much more room could have been obtained by cutting away the edge of the sternum. Gentle traction on the stitch steadied this portion of the heart wall without in the least affecting its general action. Further punctures were made with the needle, but nothing metallic could be struck. In spite of these negative findings I was very reluctant to give up the attempt to locate what I imagined ought to have been an easily identified foreign body. As a last step it was decided to inspect and palpate the back of the heart, but we found that the organ could not be lifted forward without kinking the vessels to some extent, though it could be somewhat rotated on its long axis so as to expose partially its posterior surface.

The area high up behind the ventricle was thus exposed and then the whole heart was taken into the hand so that it could be thoroughly palpated between the fingers behind and the thumb in front. As a result something hard and elongated could be felt in the very center of the viscus, presumably about the base of the interventricular septum, and this was more like our foreign body than anything else. But this examination of the whole "heart in the hand" gave us a fright, for as soon as mild pressure was applied about the base it stopped beating. It was only after a few seconds that a furtive contraction was followed by one or two others which preceded a return to the regular rhythm and it was with thankfulness that the heart was allowed to return to its normal position in the pericardium. Having failed to locate the missile by external palpation, I wondered if an exploration of the interior of the ventricle was justified.

As the bullet had not, up to the time of operation, produced any symptoms and as it could not be certainly localized, I decided that it would be unreasonable to subject the patient to the risk of opening the heart cavity and the attempt to find and remove the bullet was therefore reluctantly abandoned. The area which had been traversed by the stitch was then dealt with. The needle punctures bled just a little and might perhaps have been left alone, but it was felt safer to cover them over with a suture of fine catgut passed Lembert fashion through the visceral pericardium. This was easily done and effectively controlled the slight oozing.

A little fluid which had collected in the pericardium was gently mopped up. In spite of a good deal of tension the edges of the pericardial sac were brought together with interrupted sutures of fine catgut passed so that the visceral surfaces were in contact with each other. A small drainage tube was left in the lowest part of the sac and another laid along the outside near the suture line. When

the wet gauzes which had been used to protect the cellular tissues were removed, the emphysema of the latter was very obvious and rather embarrassing. With each expansion of the chest the pleura was forcibly advanced and it was realized how easily it might have been injured, had it not been for the gauze protection. The flap of chest wall was readily laid back into position and was held by one or two catgut sutures between the periosteum of the sternum and the perichondrial structures, but since the sternal ends of the costal cartilages had been cut away perfect apposition could not be secured. The skin was sutured with interrupted silkworm without tension, the drains being brought through the center of the lower oblique incision. The area was supported by strapping firmly applied over the dressing with an encircling chest bandage over all. The operation took one and three quarters hours, the greater part of that time being expended in efforts to locate the bullet.

The patient stood the ordeal perfectly well, though at the conclusion he was rather cyanosed, but the pulse was slow and of good volume when he left the table. Immediate recovery was satisfactory and gave no cause for anxiety. On the second and third days, with a respiration rate of 30, the pulse was over 100 but it was never more than 116 and soon came down to between 80 and 90 and then 70 and 60, and the rhythm was regular throughout. The only troublesome symptom was persistent vomiting without nausea, and this was really distressing. For days he could keep nothing down, but in spite of this seemed well and was quiet and undisturbed. In the course of a week the condition gradually subsided, having been entirely uninfluenced by treatment. The patient himself dated his revival from about the fifth day, when he expressed a great longing for a whisky and soda. Like everything else that he took this was promptly rejected, much to the discomfiture of the nurse, though the patient declared that he enjoyed it "both going down and coming up again," and he certainly began to improve from that time and eventually recovery was satisfactory. He was well enough to be out of bed in three weeks. The wound healed per primam, though the patient felt some weakness over the area and a sense of "coming apart" on coughing or exertion, but this gradually lessened and five weeks after operation, when he began to walk, the area was firmly consolidated and the chest expanding well. A month after operation Col. Beattie made an ordinary examination of the heart without finding signs of abnormality. A further x-ray made at this time showed the bullet in precisely the same position as before and moving with the heart beat, but the whirling movement which had been so striking a feature had ceased.

The patient left the hospital nine weeks after operation and thereafter steadily improved. Three weeks later the condition was good with the heart behaving well. An electrocardiogram made at this time showed the same appearances as before the operation (Fig. 5*B*). In November he reported himself as very well and shortly afterward he took up adjutant duties and next year was transferred to the records office of his regiment. After taking his discharge early in 1922, he took a long rest before resuming civilian occupation in an office. Thereafter he was able to do all ordinary things in moderation including playing a mild game of golf. Ten years after operation he married. At times he was perhaps rather apprehensive and a little too careful. In consequence he put on weight unduly and suffered from indigestion. In 1934 I had a report as follows:

". . . the heart seems to be in pretty good condition. It is not enlarged, sounds are good and the rate normal. His blood pressure about 135 . . . he has not been taking enough exercise to keep himself fit."

After that date the best epitome of his activities is that contained in a letter which I received in July, 1936, just nineteen years after the casualty.

"You will observe from the above that I have moved further North. Well, as to the past years since you heard of me—about ten years ago I obtained employment as Taxation Officer, which has proved fairly suitable for my phsyical

capacity . . . I am not required to travel much . . . I conduct the work from an office in the County town, about seven miles from this cottage, which is well in the country, and I drive myself back and forward daily in a 10 h.p. car.

"The heart has not troubled me much and so far as I can gather from such doctors as I have had to 'listen in' from time to time it appears to be working normally. I have not felt it necessary to consult a specialist at any time. Remembering the teaching, I have just been going easy physically. I have not worried about games, I mean golf, etc., for a long time. I find that with my gardening when the weather is good, I can get all the exercise I want. . . .

"As a matter of interest to you, I had my appendix removed about five years ago. A surgeon in Edinburgh did it, using a local anaesthetic. I got over it all right. I think I was back to this office in a month or five weeks. . . ."

A year later, in June, 1937, that is, just over twenty years from the time of the casualty, I had the pleasure of a visit from the patient, when the following note was made:

"The Captain came to see me. He is now staying in London for a little holiday. He informs me that on the whole he is very well and has no disability of any sort so far as his heart is concerned. He still lives in the country and usually drives his own car to his office, but when the weather is fine, he walks one and a half miles to the nearest village and gets a 'bus, but he does not do that in cold weather. During recent years he has been occupied in making a garden and works a good deal himself. He gave up golf a few years ago, not because he found it did any harm but because he thought it would perhaps be wiser not to exert himself unduly.

"At times he has suffered from indigestion, or what he calls indigestion, which has taken the form of a pain in the epigastrium, but it has never been very bad.

"He is now fifty-two years of age, and looks very well though rather heavy and with an obese abdomen. The scar over the pericardium looks perfectly normal in every way; it is firm and gives no trouble. The Captain made no complaint except of his ear, which was troubling him a good deal. Dr. Duncan White made an x-ray examination and reported:

" 'A bullet is embedded in the wall of the left ventricular septum. Its movement is synchronous with the cardiac contractions. There is slight enlargement and rounding of the left ventricle with very slight unfolding of the aorta.' " (Fig. 4.)

Dr. R. S. Aitken, now Professor Aitken of Aberdeen, made an examination of the chest, and except for some emphysema there were no signs of disease. The heart appeared to be normal and the pulse ranged about 62 and was perfectly steady. The blood pressure in three readings averaged 138/88. At the same time Dr. Paul Wood made an electrocardiogram which he reported as being entirely within normal limits (Fig. 6). At the same time I took the opportunity of asking Dr. Wood to let me have his observations on the previous electrocardiograms, that is, those made just before and just after the exploration, as I knew that much light had been thrown on cardiographic problems since the time the patient first came under observation. The following is his comment:

"These electrocardiograms, showing inversion of the T wave in Leads 1 and 2, often with a diphasic effect, probably signify haemopericardium in the first instance and healing of it in the second. Alternatively they might indicate an injury to the anterior wall of the left ventricle. If the bullet entered the left ventricle anteriorly it is impossible to say whether the muscular injury or the associated pericardial lesion was the cause of the electrocardiographic findings, but it was certainly one or the other. If the bullet did not damage the anterior wall of the left ventricle, then the pericardial lesion can be blamed with certainty. Not much blood in the pericardial cavity would be necessary.

"The graphs are, of course, quite abnormal, and I can say with certainty that there could be no other cause for them in this case. They are rather more like the changes due to haemopericardium or to other pericardial conditions than those of anterior left ventricular injury. . . ."

In April of this year (1940)* the patient reported that he was quite well, though he confessed to being a little tired, "a result of the present war, not the last one!" When fatigued he suffers from what he describes as indigestion, but this passes off after a week or ten days' rest.

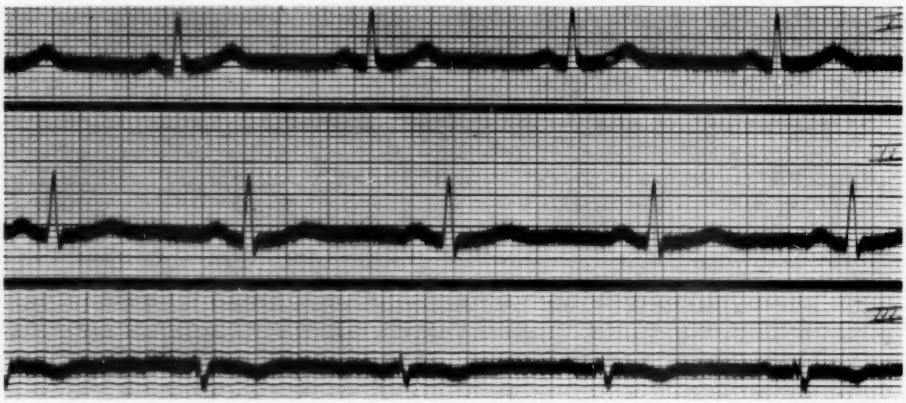

Fig. 6.—Normal electrocardiogram with bullet in situ in left ventricle twenty years after casualty.

Considering the magnitude of the last great war with its multiplicity of arms and its huge toll of casualties, it is surprising that there are comparatively few records of patients long surviving with bullets lodged in the heart. That there are still fewer cases where a fragment of shell has been retained is almost certain, because wounds caused by these fragments are so frequently fatal as a result of infection. Further, many foreign bodies supposed to be in the heart are really imprisoned in some part of the pericardium. In a recent review of the subject Decker[1] was able to quote from 100 case reports of foreign bodies retained either in the heart or pericardium and of these 65 were bullets or fragments of shell in the heart itself. Probably there are many more examples than have been recorded and some indeed may be unknown, for, strange though it may seem, there are those who were wounded in the late war who have never been submitted to x-ray examination. All those who have looked into this matter have been struck by the number of cases in which portions of missiles imprisoned in the heart have apparently not given rise to inconvenience much less serious symptoms, a wonderful tribute to nature's powers of repair. In his interesting review of "Specimens Showing the Effects of Gunshot Injury on the Heart and Blood Vessels in the War Collection at the Museum of the Royal College of Surgeons of England" Makins[2] suggests that bullet wounds of the ventricles need not necessarily end in fatality. It should be observed that wounds of the auricle are different, for the

*April, 1941, patient very well just twenty-four years after the casualty.

walls of those cavities are so much thinner and so easily torn that death from hemorrhage is to be expected. Nonetheless, in Decker's series no less than 8 of the examples of the 65 retained missiles were in the auricles. As the result of his review and of his great experience in military surgery, Makins suggested that when death was immediate it was as likely to be due to shock as to hemorrhage. He also stated that probably a spent bullet would be much more likely to lodge in the heart. This point is strikingly illustrated by the case reported by Birkbeck, Lorimer, and Gray[3] in which a bullet was lodged in the right ventricle. In that case the bullet had "passed through and killed a man in front of him."

In the case now reported there is no certain information as to the distance which the bullet traveled before striking its victim, but the fact that it probably traversed the upper arm and certainly the large wad of paper material in the breast pocket was probably enough to slow up its velocity and possibly determine its lodgment. (The ventricular wall may be perforated by a missile not only without serious hemorrhage into the pericardium but with practically no bleeding.) The impaction of the bullet in the heart wall may act as a plug and in some cases[4] the bullet has actually been found so situated, the base projecting slightly from the outer cardiac wall. Deposit of clot around the bullet may also play a part, but probably the powerful contraction of the heart muscle is the most important factor. Anyone who has witnessed the extreme contractile power of the heart muscle in vivo will have no difficulty in realizing that this in itself would probably be enough to close the tract of the bullet and to prevent any but trivial hemorrhage; this is certainly borne out by the experience of this case. At the operation there was only a small amount of blood-stained fluid in the pericardium and no evidence that there had ever been free hemorrhage. In stab wounds of the heart (Fig. 7) the condition seems to be rather different for there is usually free bleeding, but even so the actual loss of blood is often not enough in itself to kill the patient, death usually occurring because the collection of blood in the pericardium compresses the heart and leads to the condition known as "cardiac tamponade," which is usually the cause of the immediate fatality. When a bullet is lodged in the heart wall without causing immediate mortality, what is the reaction of the surrounding tissues to the intruder? It may be safely asserted that in the absence of infection encapsulation by fibrous tissue will occur.

That this process was taking place was suggested in the case under consideration by the fact that the whirling movements at first seen on fluoroscopic examination gradually ceased as though that part of the bullet projecting into the heart cavity were becoming gradually covered by organizing clot which would be provided by a smooth endothelial covering. Exactly the same thing appears to have occurred in the case

recorded by Burgess.[4] I have not been able to find an illustrative specimen either in the Museum of the Royal College of Surgeons of England, the Army Medical Museum at Millbank, or the Museum of the Medical School at Newcastle-on-Tyne. But the state of the parts has been mentioned by some surgeons, and Couteaud and Bellot,[5] recording a case where a bullet was lodged in the wall of the auricle from May 14 to Nov. 9, state that "the vigorous fibrosis which surrounded the

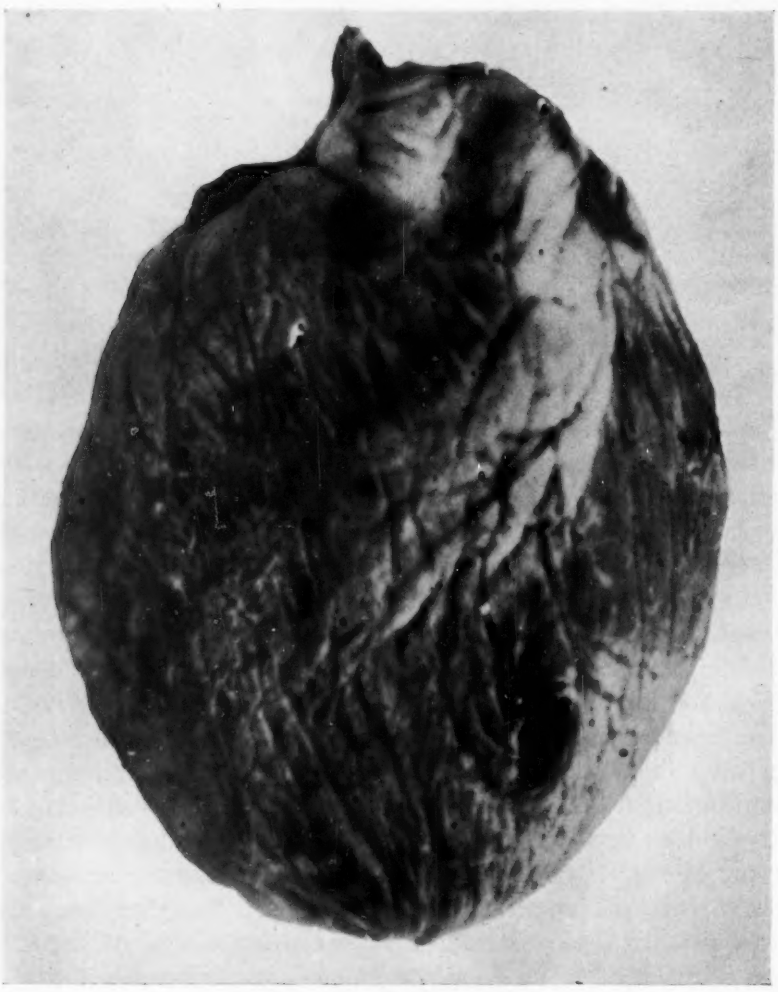

Fig. 7.—Stab wound of left ventricle produced by an Arab dagger.

bullet resembled a veritable fibroma, its capsule averaging 1½ centimetres in thickness." In another published case the bullet is said to have become encysted. In the Museum of the Army Medical College at Millbank there is a specimen of a heart with a piece of the anterior pericardium and lying on the outer surface of the latter, just opposite the root of the great vessels, is an old-fashioned lead musket ball (Fig. 8). The catalogue description states that the man was wounded in New

Zealand in 1860. "There were doubts as to whether or not the bullet had penetrated the chest so trifling were the symptoms." The man lived for fourteen years and then died in Ashantee from remittent fever when the bullet as shown in the specimen was disclosed at the post mortem.

It is surprising that many missiles have remained quite free in the cavities of the heart, from which they have been removed at considerable intervals after the casualty and often with success. When loose in the cavities, they may leave the heart with the blood stream and become lodged in one of the great vessels. Indeed there seems to be no end to the vagaries of these unattached and unwelcome visitors. On the

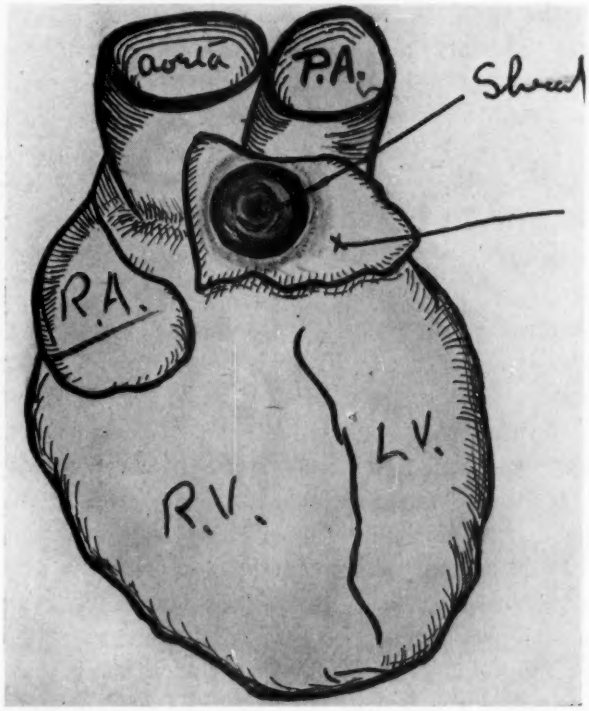

Fig. 8.—Leaden ball encysted outside pericardium and discovered at post mortem fourteen years after wound. At the time of the casualty the symptoms were trifling. Death was the result of a tropical fever. (From Army Medical Museum, Millbank.)

other hand, a wound in the heart, however produced, may result in a weak scar which may subsequently rupture either spontaneously or as the result of violence or may gradually yield, to be followed by the development of an aneurysm of the viscus. Late dislodgments of a foreign body may also occur. The symptoms associated with impacted foreign bodies which have produced neither immediate nor rapid death and have settled down in the organ also vary. The case under consideration shows that there may be an entire absence of symptoms and, indeed, except for the disclosure of the x-ray, the presence of such a thing as a foreign body in the heart might well be doubted. It is recorded (Decker) that some patients who harbor foreign bodies in the

heart have done heavy work, such as coal heaving, and that one man climbed a mountain 2,000 meters high. On the other hand there may be attacks of palpation, irregularity of heart action, and dyspnea or syncopal attacks on exertion. In some cases pain has been a marked feature, either precordial or retrosternal and either sharp or dull. Sometimes the trouble is more a sense of oppression over the heart. In some cases the symptoms follow close on the injury, but as a rule such early troubles settle down as the result of the long period of rest which is enjoined and in about one or two years cases that are going to do well should be symptom free. In others the symptoms only occur when an attempt is made to resume active normal life. The differences in the consequences probably depend on the position of the foreign body in the heart and especially its relation to the muscle bundles and the co-ordinating centers. In addition to the characteristic cardiac symptoms just mentioned there may be neurotic manifestations which mainly depend on the attitude of the patient to the knowledge that he harbors a foreign body in one of the citadels of his well-being. Patients who have felt no evil consequences have sometimes been kept in thralldom by the well meaning attentions of overanxious relatives or friends.

The management of these cases is a matter for serious consideration. A patient who has fortuitously survived a casualty so menacing deserves to be very closely guarded against ill-advised attempts at surgical intervention. In the case which is here recorded the attempt to remove the missile appeared to be justified for the reasons already stated, but at that time there was little to guide us as to the natural history of bullets in the heart. The experience that has since accumulated has shown that in the process of time many foreign bodies, perhaps most, become safely encysted and do no harm. The fear of infrequent late complications (Decker quotes Loisson that there were 9 cases of late rupture of cardiac aneurysm in 254 cases of heart injury) should not be made an excuse for intervention when the patient is symptom free, and it would seem a good rule to leave the foreign body alone unless the heart continues to rebel against its presence. The interpretation of the disclosures of the electrocardiograph may furnish some guide as to when intervention is in the best interests of the patient. On the other hand, if definite symptoms persist or develop, then intervention of course, should be seriously considered, and the operation for removal of missiles from the heart has now many brilliant successes to its credit. The situation of the foreign body has a decided bearing on the question, for those situated in the ventricles or near the apex have proved much easier problems than when the auricles are involved or when the lodgment is in the posterior surface of the organ. I am not here and now concerned with the question of foreign bodies in or about the pericardium, but it may be observed that in those cir-

cumstances the problem is entirely different. If a foreign body in the pericardium is causing symptoms, it ought to be possible to remove it comparatively easily and with little risk, and no competent surgeon need hesitate to undertake the intervention. In two cases (Figs. 9 and 10) in which I operated the foreign body was the cause of an external sinus. Both were imbedded in the pericardium, and it was not difficult to remove them, using an incision by the side of the sinus and excising cartilage. For merely opening the pericardium for purposes of exploration or for removing a loose body in that cavity, an incision in Larry's angle ought to be very satisfactory. When the foreign body is fixed and anterior, it may be reached by the nearest route from the surface, which will usually mean making a parietal incision along one of the lower costal cartilages on the left side. Should the missile be

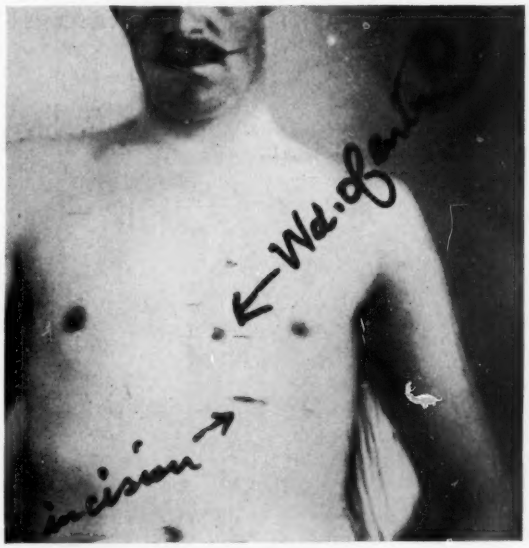

Fig. 9.—Bullet wound over pericardium. Patient wounded in November, 1916. Free discharge of pus from the track which healed and broke down many times. Removal of foreign body in August, 1917, followed by good recovery with complete healing.

on the posterior surface or the lateral walls, the Kocher approach is probably the best. I have no experience in the extraction of the foreign body under the fluorescent screen, a small incision having been made into the pericardium from the surface of the chest. This is a method suggested and practiced with success by some French surgeons. In fortunate circumstances this may be successful, especially with a foreign body loose in the pericardium and sometimes perhaps if the foreign body is merely attached to the outer surface of the heart, but I cannot imagine it being successful in other circumstances. Just prior to any operation for the removal of a foreign body, the exact position of the object must be again confirmed by careful x-ray examination. It is quite remarkable how the movements of the heart may be communicated to a foreign body which is not really in that organ. On occasion

it may require great knowledge and skill on the part of the radiologist to state with assurance the exact situation of foreign bodies about the heart. The technique of operative intervention turns largely on the question of exposure. Although general anesthesia has usually been employed, many operations have been successfully carried out under local anesthesia alone. A whole variety of methods can be employed and they fall into two groups (1) those where the approach

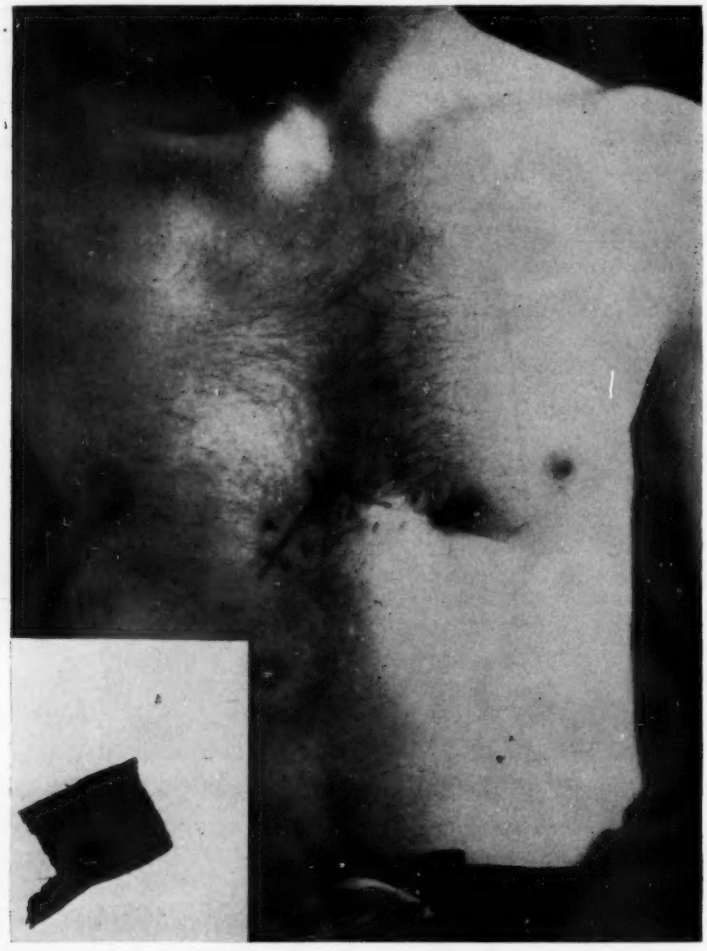

Fig. 10.—Gunshot wound over pericardium. Patient wounded in June, 1916; thereafter wound healed and broke down many times. Seen June, 1918, with foul discharge from the sinus, the mouth of which was tucked in with every heart beat. Excision of two cartilages with removal of foreign body (shown in insert) resulted in complete recovery.

is parasternal represented by (a) the original Kocher flap method, (b) cartilage and rib resection, (c) the intercostal approach where the ribs are spread and the pleural cavity opened, (2) the trans-sternal approach in which the body of the sternum is vertically divided and the halves forced apart; as a modification it has been suggested that the body of the sternum may be removed. The method to be employed is largely decided by the part of the heart which it is desired to explore.

The parasternal approach of Kocher gives an admirable exposure of both ventricles and the lower part of the auricles and by lifting up and rotating the organ its posterior surface can be reached. The trans-sternal approach gives a freer exposure of the auricles, especially the right. The original plan of Kocher was employed in the case here recorded and proved very satisfactory. From my experience with this case and the study of dissections made for me by my colleague, Mr. A. K. Henry, I feel satisfied that it is efficient. Study of the exposure of the dead rigid immobile heart as found in the cadaver is illusionary. The living organ is more accommodating for it stands forward in a striking way, but the difference in size when the organ is in systole is very remarkable, nonetheless, its constant movement is embarrassing. As Kocher always insisted, every surgeon ought to be prepared to expose the heart in emergency and for most general purposes the method associated with his name will prove satisfactory. In these times it may not be inappropriate to set out the steps of this useful operation. These are as follows:

1. Incision from center of sternum along sixth costal cartilage as far as the mammary line. This divides all the soft structures down to the cartilages, including the costal attachment of the rectus abdominis.

2. Separation of the perichondrium and excision of the cartilage, the separation to be commenced at the sternal end, the junction with the seventh cartilage being divided. This exposes the mammary artery and vein a finger's breadth from the edge of the sternum. These vessels should be ligatured and divided.

3. Make a vertical incision through the triangularis sterni muscle close to the sternum.

4. Gently thrust this muscle outward. This will carry the pleura out of harm's way and expose the pericardium which can be opened either now or at a later stage.

6. To secure more room, make a vertical incision up middle of sternum to level of third or even second rib; in a bulky subject make an incision along one or other of these cartilages for three or four inches.

7. Separate the periosteum of the sternum outward until costal cartilages are exposed.

8. Separate the intercostal muscles from the borders of the cartilages and gently insinuate finger behind each just by edge of sternum. Divide fifth, fourth and third cartilages at their inner ends.

9. Lift up flap with a view to turning it back to the left. Do this slowly and gently push pleura outward as the cartilages are elevated.

10. Break cartilages at junction with ribs, thus exposing a considerable area of pericardium.

11. Carefully palpate state of affairs through pericardium.

12. Open pericardium along edge of sternum and, if necessary, outward at lower end of exposure.

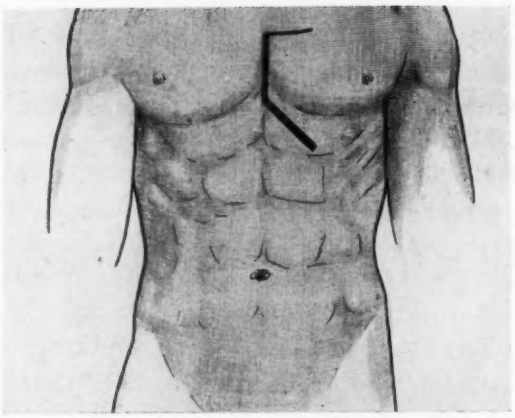

Fig. 11.—Incision for exposure of the heart. The primary incision along the sixth rib is indicated by a broad line, while the transverse cut along the third (or second) rib is represented by a finer line. (Modified after Kocher.)

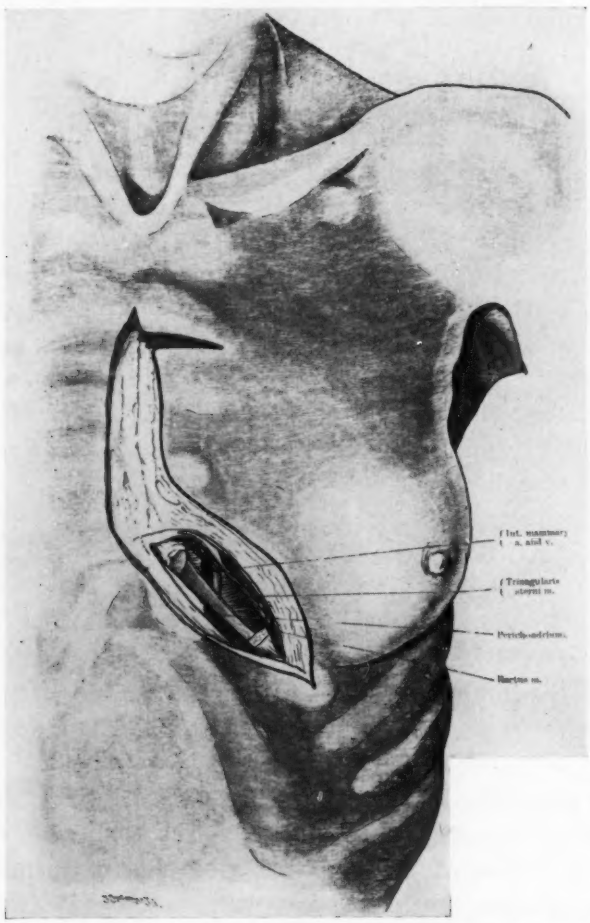

Fig. 12.—Exposure of the heart. The skin and fascia are divided, and the sixth costal cartilage resected. The perichondrium is exposed lying on the triangularis sterni, on which also the internal mammary vessels descend. (Modified after Kocher.)

13. To secure further space use rongeur forceps to cut away remains of sternal ends of costal cartilages and, if required, part of the sternum.

These steps are shown in Figs. 11, 12 and 13, slightly modified from Kocher's well-known textbook on *Operative Surgery*. The great thing is to work from below to keep near to the sternal edge and to push the structures gently outward. It assists separation of the pleura if some local anesthetic is injected into the extraperitoneal tissues.

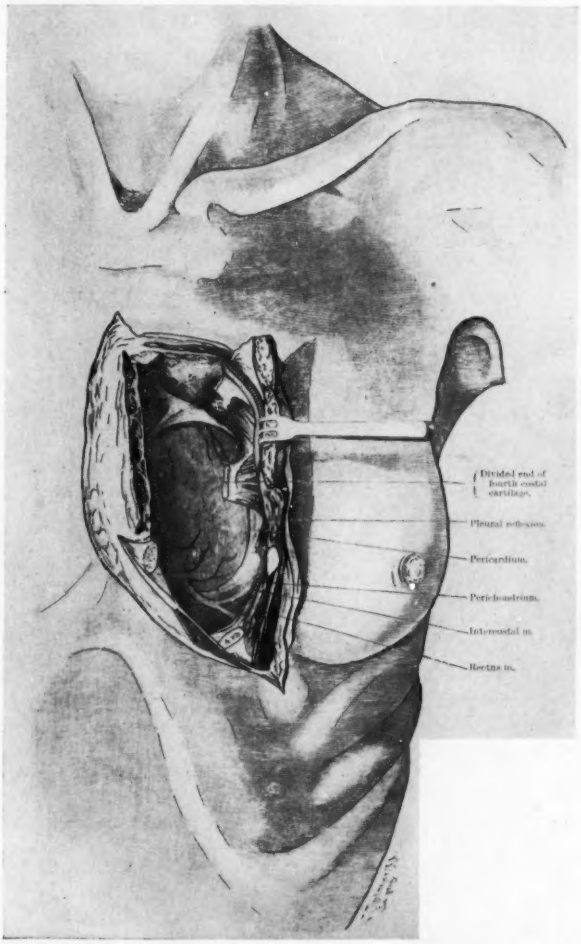

Fig. 13.—Exposure of the heart. The sixth rib is resected; the fifth, fourth, and third costal cartilages are divided and retracted outward along with the pleural reflexion (after division of the triangularis sterni). The internal mammary vessels are seen ligatured and divided, and the pericardium is fully exposed. (Modified after Kocher.)

The intercostal approach with free opening of the pleural cavity exposes the patient to all the risk of pneumothorax without compensating advantages. Though the method is rapid, it must be remembered that some form of positive pressure anesthesia should be employed. In the presence of a pneumothorax with a wound of the lung the method is ideal. The fourth costal cartilage and corresponding portion of the rib are excised and the pleura opened to the extent of the

incision. The space is enlarged by using the rib spreader. The pericardium is readily seen and can be opened to any required extent. At the termination of the intervention the pericardium may be closed by suture, though it is sometimes recommended that the sac should not be completely closed so that drainage can occur via the pleural cavity.

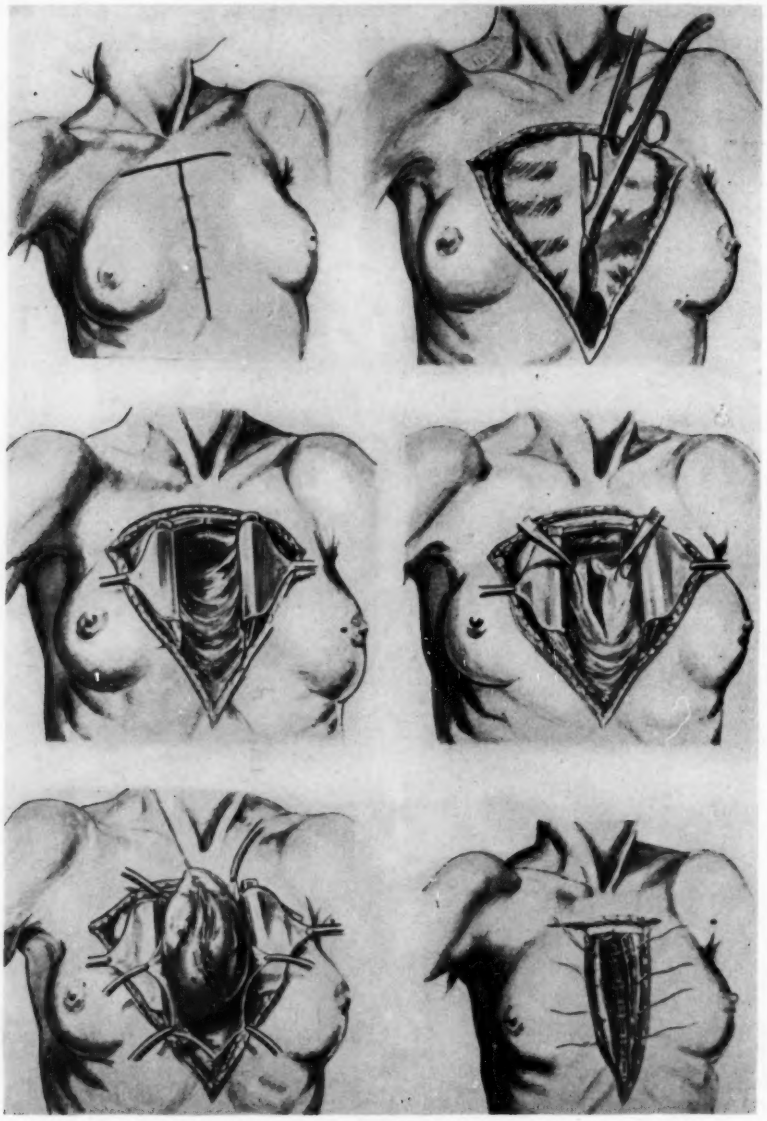

Fig. 14.—Trans-sternal approach to pericardium and heart. (After Sauerbruch and O'Shaughnessy.)

I have no personal experience with the method of splitting the sternum other than as a cadaver operation. It involves considerably more traumatism than the Kocher plan and does not appear to give as good a general exposure, though the right side of the heart is more accessible. The two halves of the bone are thrust aside by using a rib spreader (Fig. 14). When necessary, full use must be made of the

possible exposure by incision of the pericardium to the limit of the parietal incision. After exposure by any of these methods the heart may be inspected and palpated with ease so far as its anterior surface and borders are concerned. To steady the heart for more deliberate palpation or for suture or incision it is usual to put a suture into its substance near the apex; that is, where the muscle is thick and the cavity not so near the surface. This suture should be of fine silk or No. 1 chromicized catgut and must take a hold about one-third inch deep. By making gentle traction upon it, the heart may be steadied, but, if it is pulled upon, the stitch may cut out. When it comes to locating the foreign body, the utmost gentleness must be used. It is fortunate when the foreign body projects somewhat from the cardiac wall. The difficulties in locating a foreign body are sufficiently indicated by the recital of this case, but other operators have been more fortunate and doubtless more skillful. Palpation in certain areas or pushing the heart to one side or lifting it forward may cause great irregularity in the beats or even cessation. But these phenomena only continue while the abnormal stimulus is applied and when that ceases the organ usually quickly resumes its normal rhythm or does so in response to gentle stroking or very gentle squeezing applied away from the inhibiting area. All handling should be done very carefully and gently, and, if the heart shows signs of resentment, all manipulation must stop for a few moments. When the heart is to be incised, there is always the question of hemorrhage and every surgeon seems to have prepared for this eventuality by putting in sutures first and cutting between them. If profuse bleeding occurs, it may be controlled by placing the finger over the point, but great care must be taken not to thrust the finger into a softened heart. Entry of blood by the vena cava may be controlled by placing the ring and little fingers behind the base of the heart and compressing these great vessels between those fingers and the middle finger in front, thus leaving the index finger and the thumb free to carry out manipulations on the anterior surface of the organ. This maneuver is known as the Sauerbruch grip. It is said that this grip may be kept up for as long as ten minutes with safety. It is important to limit any incision into the heart muscle to the smallest proportions so that it ought to be made directly over the foreign body. It is, of course, essential to avoid injury to the coronary arteries and their branches not only when making an incision, but also in placing any sutures that may be required to close it. When the foreign body is reached, it should be grasped with strong forceps so that by a process of rotation and manipulation it may be coaxed out of a very small wound. The edges of the incision must then be closed by suture. If there is profuse bleeding, this may be somewhat controlled by crossing the guide sutures firmly over the incision while the stitches are introduced. The latter may be of fine silk or No. 000 chromicized catgut.

Should the heart muscle prove very friable a strand of suture passed parallel to the incision will act as a support for the approximating sutures, just as when used for dealing with the solid viscera. No one who has not had the experience can appreciate the embarrassment caused by the ceaseless movements of the heart. Even if bleeding does not cease at once, it will probably do so in a short time, especially if assisted by the pressure of the finger. The pericardium is closed by suture, but unless the sac has been distended the edges do not approximate very readily. Apposition is best secured by commencing at the upper extremity and carrying the suture downward. It is probably a help to interrupt the suture at a couple of points.

When there is any question of infection or of continuous oozing, it is probably safer to provide for drainage either by leaving a small tube, the edge of which is just within the pericardium, or by leaving the lower end of the incision unsutured for one-half inch. Some surgeons have had cause to regret that provision for drainage was omitted.

In the paper by Decker already referred to, he states that the late mortality of foreign bodies in the heart is about 20 per cent and that the mortality of operations for their removal has been the same. There have certainly been many brilliant achievements in this field of surgery, but probably many unsuccessful results have escaped publication and it is likely that the risks of the operation are rather understated.

The management of cases of foreign body in the heart in which the patients have survived the immediate dangers of their implantation must be settled on general surgical principles. Academic considerations and a knowledge of the fate of foreign bodies in the tissues generally would suggest a more frequent resort to operation than is wise. Nature at least should be assisted to exhibit her powers as a healer and the patients suffering from cardiac disability after gunshot wounds should have many months of rest. If, in spite of a fair chance, cardiac disability persists or develops after a period and interferes with usefulness, the aid of surgery may properly be invoked. The difficulties may be very great and even during operation a wise restraint may save a disaster. As the late Frank Jeans of Liverpool was fond of saying: "A living problem is better than a dead certainty."

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THE EXCRETION OF SULFANILAMIDE AND SULFAPYRIDINE IN HUMAN BILE*†

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AN IMPORTANT therapeutic factor possessed by sulfanilamide and sulfapyridine is the facility with which these drugs diffuse to all tissues and fluids of the body, including the liver and bile. While there is available information concerning the excretion of sulfanilamide in human bile, studies have not been recorded in the literature relative to the biliary excretion of sulfapyridine. Bettman and Spier[1] administered sulfanilamide preoperatively to each of eleven patients shortly before a cholecystectomy was done. Quantitative determinations of sulfanilamide were carried out on specimens of gall bladder bile and venous blood and they concluded from their data that the drug was excreted in the bile and concentrated in the gall bladder. Hubbard and Anderson[2] made the important observation in human subjects that, following the ingestion of sulfanilamide, larger amounts of acetylated sulfanilamide appeared in the blood as compared to the concentration in bile draining from a T-tube. Investigations of a similar nature have been made with laboratory animals. Studying the excretion of bile sulfanilamide in chronic bile fistula dogs, Carryer and Ivy[3] found that, after a single oral dose, sulfanilamide appeared in the bile within two hours and the usual maximum concentration was reached within four to six hours. They stated that the total excretion of sulfanilamide in the bile was relatively low. Observations of the same order were made by Manche, Plotner, and Siede,[4] who gave neoprontosil to dogs with bile fistulas. On the basis of their experimental studies, they administered the drug to patients with infections of the biliary tract and reported favorable clinical results.

It is apparent that more precise information is desired relative to the excretion of the sulfonamide compounds in human bile. The purpose of the present study has been to determine simultaneously the concentrations of sulfanilamide or sulfapyridine in the blood and bile under various conditions. In the manner to be described, it could be ascertained how quickly the free and conjugated forms of the compounds appeared in the bile compared to blood, when the maximum concentrations

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were reached in these media, and over how long a period of time the drugs could be detected in the bile and blood after oral administration was discontinued. Another phase of the present study depended upon the knowledge that sulfanilamide is acetylated in the liver.[5, 6] This is likewise probably true for sulfapyridine. Because of this, it appeared important to confirm and extend the observations of Hubbard and Anderson[2] and to determine whether more of the acetylated forms of both sulfanilamide and sulfapyridine appeared in the bile than in the blood.

METHODS AND MATERIALS

Essentially two methods of study were used. The first group of observations were made upon five patients who had had a cholecystectomy and choledochostomy and a T-tube inserted into the common bile duct. This permitted a collection of hepatic bile at the bedside. Several months after their operations, with the T-tubes still in place, these patients were given sulfanilamide or sulfapyridine orally and the levels of the absorbed drugs were determined simultaneously in specimens of bile and blood collected at intervals. An initial dose of 4 Gm. was administered and then 1 Gm. every four hours thereafter. It should be pointed out that the total amount of the drug excreted in the bile could not be determined, since only a part of the bile flow was diverted through the T-tube. Fortunately, there was a continuous flow of bile through the choledochostomy tubes of all the patients. The method of Marshall and Litchfield[7] was used for ascertaining the levels of the free and conjugated forms in the blood, while we employed the procedure of Doubilet, as described by Carryer and Ivy,[3] for determining the levels in the bile. The bile obtained from two patients was cultured before any drug had been administered and then again at intervals, after sulfanilamide and later after sulfapyridine had been given.

A second method of studying this problem depended upon the oral administration of acetylated sulfanilamide to seven additional patients with T-tubes in the common bile duct. Four grams of acetylsulfanilamide were given and then 1 Gm. every four hours for five doses. Simultaneous determinations of the concentration of free sulfanilamide and acetylsulfanilamide were made at intervals upon bile and blood. In this manner we desired to obtain information concerning the excretion of preformed acetylsulfanilamide by the liver. Before giving the drug to human subjects, it was administered to dogs and observations were made relative to the absorption, blood concentration, excretion, and toxic manifestations. An aqueous suspension of acetylsulfanilamide was introduced through a tube into the stomachs of two animals under fasting conditions. The concentration of both free and conjugated sulfanilamide was then determined in the blood at various intervals after the single dose had been given. In a third dog, after it received the initial large

dose of the drug, smaller does were given every four hours. Likewise, a single large dose of acetylsulfanilamide was administered to each of three human subjects and similar observations made. When it had been established that the acetylated form of sulfanilamide could be safely given to human beings, observations were then made in individuals with T-tubes.

RESULTS

Data concerning the concentrations of sulfanilamide in bile and blood are recorded in Table I. Data pertaining to sulfapyridine are presented in Table II. The outstanding finding in both groups of observations was the appreciable concentration of both sulfanilamide and sulfapyridine that was attained in bile when therapeutic doses of the drug were used. The initial levels of both sulfanilamide and sulfapyridine were lower in the bile than in the blood. It is of interest that the maximum level of bile sulfanilamide was lower than the blood sulfanilamide in all four patients. On the other hand, a much greater concentration of sulfapyridine was obtained in the bile, when compared to the blood, in two of three patients. In general, less of the conjugated forms ap-

TABLE I

CONCENTRATION OF SULFANILAMIDE IN BILE AND BLOOD

PATIENT	DOSE	HOURS AFTER INITIAL DOSE	MG. PER 100 C.C. IN BILE			MG. PER 100 C.C. IN BLOOD		
			FREE	TOTAL	PERCENTAGE ACETYLATED	FREE	TOTAL	PERCENTAGE ACETYLATED
J. B., 55-year-old female	4 Gm., then 1 every 4 hr.	4	1.0	1.04	3.85	4.94	6.0	18.4
		6	6.3	6.6	4.55	8.2	14.1	41.8
		24	15.2	16.4	7.3	16.1	28.0	42.9
		48*	11.5	13.0	11.5	18.2	21.7	16.1
		72	9.2	9.3	10.2	9.5	12.1	27.4
	Total, 16	96	3.2	3.4	5.9	4.0	5.0	20.0
		120	1.0	1.1	9.2	Trace	1.0	---
F. W., 49-year-old female	4 Gm., then 1 every 4 hr.	4	5.0	5.2	3.85	18.2	23.0	20.8
		6	13.3	13.7	2.9	15.2	23.3	34.7
		24	13.4	13.6	1.5	14.5	20.0	27.6
		48*	8.6	9.8	12.2	10.5	16.0	34.4
		72	7.8	8.8	11.3	3.87	8.0	51.2
	Total, 16	96	Trace	Trace	---	Trace	1.66	---
		120	Trace	Trace	---	Trace	1.9	---
O. H., 68-year-old male	4 Gm., then 1 every 4 hr.	16	6.7	8.2	18.3	11.9	14.7	19.0
		40	7.4	8.6	14.0	11.8	20.0	41.0
		64	8.7	8.9	2.25	15.5	20.0	22.5
		88*	8.8	10.4	15.4	16.5	23.4	29.5
		112	3.35	3.9	14.0	3.85	8.35	54.0
	Total, 20	136	1.23	1.47	16.3	Trace	4.05	---
		160	1.39	1.46	4.8	Trace	5.10	---
		184	1.10	1.27	13.4	Trace	5.3	---
		208	Trace	Trace	---	Trace	2.14	---
R. N., 47-year-old male	4 Gm., then 1 every 4 hr.	16	---	---	---	9.5	13.8	31.1
		24	2.2	2.4	8.3	9.2	10.1	8.2
	Total, 14							

*Sulfanilamide discontinued.

peared in the bile than in the blood. This was true for both sulfanilamide and sulfapyridine. Patient J. B. (Table II) had very high concentrations of bile sulfapyridine, with relatively small amounts present as the conjugated form. This patient had a moderately severe systemic reaction following the ingestion of the drug. She had chilly sensations, severe headache, and marked nausea, but no vomiting.

TABLE II

CONCENTRATION OF SULFAPYRIDINE IN BILE AND BLOOD

PATIENT	DOSE	HOURS AFTER INITIAL DOSE	MG. PER 100 C.C. IN BILE			MG. PER 100 C.C. IN BLOOD		
			FREE	TOTAL	PERCENTAGE ACETYLATED	FREE	TOTAL	PERCENTAGE ACETYLATED
J. B., 55-year-old male	4 Gm., then 1 every 4 hr. Total, 5	4*	5.6	5.8	3.5	8.5	11.2	23.7
		6	38.5	43.5	11.5	11.6	13.6	14.7
		24	51.3	51.3	0.0	17.9	19.6	8.7
		48	6.4	7.9	19.0	3.8	6.2	37.8
F. W., 49-year-old female	4 Gm., then 1 every 4 hr. Total, 5	4*	0.0	0.0	0.0	7.3	11.0	33.7
		6	0.0	0.0	0.0	9.3	12.7	26.8
		24	8.5	9.0	5.6	8.5	12.4	31.4
		48	6.2	6.5	4.6	2.6	4.2	38.2
J. Bl, 61-year-old male	4 Gm., then 1 every 4 hr. Total, 10	4	0.0	0.0	0.0	3.1	4.0	22.5
		6	5.2	5.4	3.7	4.9	6.4	23.4
		24*	20.4	24.4	16.4	7.6	10.4	26.8
		48	12.6	12.8	1.6	7.4	10.1	26.7

*Sulfapyridine discontinued.

A culture of *E. coli* was obtained from bile specimens of Patients J. B. and F. W. (Tables I and II) before they received any drug. Following the administration of sulfanilamide, and later following sulfapyridine, this organism was still present in the bile of both patients. It is noted that Patient J. B. had a level of 51.3 mg. of sulfapyridine per 100 c.c. of bile.

When a single, large dose of acetylsulfanilamide was administered orally to dogs, an appreciable concentration of this form of sulfanilamide was attained in the blood (Table III). It is of interest that small amounts of free sulfanilamide appeared in the blood, indicating some degree of hydrolysis of acetylsulfanilamide in the animals' bodies. Table IV shows a larger number of observations made upon a third animal receiving divided doses of acetylsulfanilamide. No toxic manifestations were apparent in any of the dogs. The acetylated form of sulfanilamide was readily recovered from the urine and also free sulfanilamide in smaller quantities. These observations in dogs are in agreement with the previous studies of Marshall and his associates[8] and with those of Ockerblad and Carlson.[9]

Acetylsulfanilamide was then administered orally to three human subjects in order to compare the effects of the drugs with the observa-

TABLE III

BLOOD CONCENTRATIONS OF FREE AND ACETYLATED SULFANILAMIDE IN ANIMALS RECEIVING SINGLE DOSE OF ACETYLSULFANILAMIDE

DOG NO.	WEIGHT (KG.)	DOSE (GM.)	TIME AFTER INITIAL DOSE	MG. OF SULFANILAMIDE PER 100 C.C. OF BLOOD	
				FREE	ACETYLATED
1	15.4	8	30 min.	Trace	3.78
			1 hr.	0.47	7.53
			2 hr.	0.58	12.42
			3 hr.	0.90	17.60
			4 hr.	0.93	14.67
			6 hr.	0.97	12.03
			8 hr.	1.44	10.86
			24 hr.	0.65	1.17
2	20.4	4	30 min.	0.0	1.8
			1 hr.	0.0	2.44
			2 hr.	0.0	4.78
			3 hr.	0.50	6.60
			4 hr.	Trace	6.60
			5 hr.	Trace	7.15
			8 hr.	0.32	5.68
			24 hr.	Trace	1.15

tions made in dogs. The results showing the blood concentrations of sulfanilamide are presented in Table V. Again, small amounts of free sulfanilamide appeared in the blood. The maximum concentration of acetylated sulfanilamide in the blood was reached within the first six hours after receiving a single dose and declined slowly thereafter. Urine was collected over the first twenty-four-hour period for Subjects H. B. and B. N. The urine from Patient H. B. contained 2.95 mg. per 100 c.c. of free sulfanilamide and 57.5 mg. of acetylated sulfanilamide. The

TABLE IV

CONCENTRATIONS OF FREE AND ACETYLATED SULFANILAMIDE IN THE BLOOD AND URINE OF AN ANIMAL RECEIVING DIVIDED DOSES OF ACETYLSULFANILAMIDE

DOG NO.	WEIGHT (KG.)	DOSE	TIME AFTER INITIAL DOSE	MG. OF SULFANILAMIDE PER 100 C.C. URINE		MG. OF SULFANILAMIDE PER 100 C.C. BLOOD	
				FREE	ACETYLATED	FREE	ACETYLATED
3	16.3	8 Gm.,	30 min.	2.20	0.58	Trace	1.12
		then 1	1 hr.			Trace	2.47
		every 4	2 hr.	3.40	21.30	0.33	2.95
		hr.	3 hr.	4.17	52.73	0.40	4.20
			4 hr.	2.57	51.83	0.38	8.92
		Total, 13	6 hr.	2.84	50.46	0.58	12.32
			8 hr.			2.68	13.92
			12 hr.			2.55	18.25
			16 hr.			2.57	16.33
			20 hr.*			2.74	15.16
			24 hr.			3.06	15.44
			28 hr.			2.65	10.25
			32 hr.			2.98	9.82
			36 hr.			2.14	7.06
			48 hr.			1.38	3.42
			56 hr.			1.13	0.49
			72 hr.			0.52	0.84

*Acetylsulfanilamide discontinued.

TABLE V

CONCENTRATIONS OF FREE AND ACETYLATED SULFANILAMIDE IN HUMAN SUBJECTS RECEIVING ACETYLSULFANILAMIDE

HUMAN SUBJECT	DOSE (GM.)	TIME AFTER INITIAL DOSE	MG. OF FREE SULFANILAMIDE PER 100 C.C. OF BLOOD	MG. OF ACETYLATED SULFANILAMIDE PER 100 C.C. OF BLOOD
W. D., 17-year-old male	4	1.5 hr.	0.248	5.0
		3 hr.	0.291	4.95
		4 hr.	0.216	4.72
		6 hr.	0.458	4.25
H. B., 16-year-old male	6	30 min.	Trace	3.67
		1 hr.	Trace	3.54
		2 hr.	0.44	5.36
		3 hr.	0.42	5.30
		4 hr.	0.53	4.59
		6 hr.	0.47	4.80
		8 hr.	0.36	3.99
		24 hr.	0.36	2.34
		48 hr.	Trace	1.53
		72 hr.	Trace	1.01
		96 hr.	0	0.58
		120 hr.	0	1.18
B. N., 27-year-old female	6	30 min.	Trace	2.17
		1 hr.	Trace	4.70
		3 hr.	0.36	4.79
		4 hr.	0.40	2.42
		6 hr.	0.50	1.60
		8 hr.	0.50	1.70
		24 hr.	0.38	1.02
		48 hr.	Trace	0.44

total amount of sulfanilamide recovered in this period was 1.03 Gm. A twenty-four-hour collection of Patient B. N. had 4.65 mg. per 100 c.c. of free sulfanilamide and 83 mg. of the acetylated form with a total recovery of 1.92 Gm. These observations confirm those of Ockerblad and Carlson.[9] All three individuals tolerated the drug well. Patient B. N. (Table V) complained of a headache several hours after receiving the drug. None showed any evidence of cyanosis, and methemoglobin was not detected spectroscopically in blood samples.

Having established to our own satisfaction that acetylsulfanilamide could be safely administered to human subjects, the compound was given orally to seven individuals having T-tubes in the common duct. They were given a total of 20 Gm. in twenty hours. None of the patients had any appreciable manifestations of toxicity. At another period, these same subjects had received equivalent doses of sulfanilamide and the amounts of free and acetylated sulfanilamide quantitated in the bile and blood. Comparative results, showing the concentrations of free and acetylated sulfanilamide in the bile and blood when sulfanilamide had been administered, and also the results after acetylsulfanilamide had been given, are shown in Table VI. Attention is called to the fact that, following the exhibition of sulfanilamide, only small quantities of the

TABLE VI

COMPARATIVE STUDY OF EXCRETION OF SULFANILAMIDE AND ACETYLSULFANILAMIDE IN HUMAN BILE

PATIENT	HOURS OF COLLECTION	SULFANILAMIDE				ACETYLSULFANILAMIDE			
		BLOOD (MG. PER 100 C.C.)		BILE (MG. PER 100 C.C.)		BLOOD (MG. PER 100 C.C.)		BILE (MG. PER 100 C.C.)	
		FREE	CONJUGATED	FREE	CONJUGATED	FREE	CONJUGATED	FREE	CONJUGATED
J. W., 41-year-old female	4	7.4	8.72	1.4	0	Trace	8.4	Trace	2.5
	21	6.53	7.57	7.59	Trace	Trace	10.52	1.51	2.87
D. L., 74-year-old female	4	1.6	1.0	Trace	Trace	1.6	6.7	1.8	1.7
	20	8.7	6.2	5.2	Trace	2.0	11.2	1.4	5.4
L. B., 47-year-old female	4	4.39	10.31	3.49	Trace	4.4	8.5	1.4	1.9
	21	11.3	8.3	9.28	Trace	1.8	11.1	1.4	2.9
A. K., 63-year-old male	4	9.1	3.0	Trace	Trace	Trace	2.8	Trace	Trace
	20	9.0	3.5	3.4	Trace	Trace	3.78	Trace	2.36
M. A., 61-year-old female	4	6.0	2.3	3.1	Trace	2.0	6.7	1.0	2.9
	20	10.2	5.7	4.8	Trace	1.9	12.3	1.1	6.3
B. L., 57-year-old male	4	2.6	1.0	Trace	Trace	Trace	4.3	Trace	1.2
	21	10.3	4.0	7.6	1.0	Trace	6.7	Trace	2.0
H. B., 36-year-old male	4	7.1	2.6	4.9	Trace	Trace	5.7	Trace	Trace
	21	6.4	7.9	5.6	1.0	1.2	7.0	1.2	3.1

conjugated form of sulfanilamide appeared in the bile as compared to the blood. On the other hand, when acetylsulfanilamide was administered, higher concentrations of this form were present in the bile, but in no instance did it reach the levels present in the blood. It is also apparent that part of the acetylsulfanilamide was hydrolyzed in the body since free sulfanilamide was detected in the blood and bile after acetylsulfanilamide had been administered.

DISCUSSION

It may be concluded from the foregoing data that appreciable concentrations of sulfanilamide and sulfapyridine may be obtained in human bile when therapeutic doses are administered orally. Although the number of observations made is small, it is of interest to note the high concentrations of sulfapyridine found in the bile of two individuals as compared to the blood, and yet a higher percentage of the conjugated form was present in blood samples. Marshall and Litchfield[10] have pointed out that, following the administration of sulfapyridine to dogs, higher concentrations of the drug were found in the liver than in the blood. This was not true for sulfanilamide. Since Stewart and his associates[11] observed that over 90 per cent of ingested sulfanilamide may be recovered in the urine; since it has also been found that the kidneys are the main excretory channel for absorbed sulfapyridine,[12] it is not unlikely that, after the compounds are excreted in the bile, they are reabsorbed to a considerable extent from the intestinal tract.

This study has brought forth further information concerning the excretion of these compounds. It is now generally agreed that at least partial acetylation of sulfanilamide and sulfapyridine takes place in the liver. The present observations reveal that lower concentrations of the conjugated products are found in the bile than in the blood, even when pre-formed acetylated sulfanilamide is brought to the liver. It would appear that acetylation is a protective phenomenon whereby the organism attempts to convert a toxic substance into one which, though not less toxic, is more readily eliminated through the kidneys. Conjugated sulfanilamide and sulfapyridine are cleared more rapidly through the kidneys than the free forms.[11, 12]

Since appreciable levels of sulfonamide compounds may be obtained in the bile when administered orally or parenterally, it would be anticipated that the drugs would be of value in the treatment of infections of the biliary tract. A few clinical reports bear this out and in a few instances we have noted striking improvement following the administration of sulfapyridine. Manche, Plotner, and Siede[4] successfully utilized prontosil and neoprontosil in the treatment of patients with cholangitis, cholecystitis, and hepatitis. Some of their patients were jaundiced before therapy was instituted. Herrell and Brown[13] treated two cases of

cholangitis and one case of jaundice with neoprontosil. They did not present the results of this therapy but stated that the drug did not cause any evidence of hepatic damage. Cleveland[14] administered neoprontosil and sulfanilamide to a patient with severe cholangitis, marked liver damage, and jaundice and ascribed recovery of the patient to chemotherapy. Only a few instances are recorded where the sulfonamides have been used in the treatment of patients with biliary typhoid and paratyphoid infections. Bazin[15] had a patient from whom paratyphoid B bacilli were consistently isolated from the bile and feces. He was successful in eradicating the infection with sulfanilamide. On the other hand, Lembcke[16] failed in an attempt to treat a typhoid carrier after apparently adequate doses of sulfanilamide had been used.

Although sulfanilamide and its derivatives may prove useful in the treatment of certain suppurative conditions of the biliary tract, these drugs must be administered cautiously to patients with liver injury.[17] Watson and Spink[18] have observed that a majority of patients receiving the usual therapeutic doses of sulfanilamide had a resultant temporary hepatic dysfunction. They noted that, when the drug was given to patients who had evidence of liver damage before therapy was started, there was an increase in the degree of liver dysfunction coincident with the administration of the drug.

Finally, the colon bacillus is one of the most commonly found microorganisms in suppurative conditions of the biliary tract. In the present study, it was observed that this organism persisted in the bile of two patients even after high concentrations of sulfanilamide and sulfapyridine had been maintained for several days. There are some strains of this organism that are notoriously resistant to the action of sulfanilamide. Therefore, in treating patients who have infections of the biliary tract and hepatic injury with sulfanilamide or its related compounds, one may be faced with the likelihood of failing to affect the infection and at the same time producing further hepatic damage.

SUMMARY

1. Sulfanilamide and sulfapyridine were administered to patients several months after performance of a cholecystectomy and choledochostomy, accompanied by T-tube drainage of the common bile duct. This procedure permitted the collection of bile specimens.

2. Appreciable concentrations of sulfanilamide and sulfapyridine were attained in hepatic bile when compared to the blood levels.

3. Lower levels of the conjugated forms were present in the bile than in the blood.

4. Administration of acetylsulfanilamide to human subjects resulted in lower concentrations of this compound in hepatic bile than in blood.

5. The use of the sulfonamide compounds in the treatment of infections of the biliary tract is discussed.

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THE VALUE OF THE LOCAL IMPLANTATION OF CRYSTALLINE SULFANILAMIDE ABOUT GASTROINTESTINAL ANASTOMOSES IN DOGS*

A Valuable Adjunct in the Prevention of Peritonitis

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FOR THE PAST two years studies have been in progress upon the physiology of gastric secretion at the Experimental Laboratory, Department of Surgery, University of Minnesota. During the process of these investigations more than 250 operations were performed upon the gastrointestinal tract of the dog. Despite the development of a method[1] of closed gastrojejunal anastomosis, which in the clinic was accompanied by a mortality of less than 2 per cent for gastric resections for ulcer and less than 10 per cent for gastric resections for carcinoma, the procedure on the dog was by no means so successful. The mortality in the dog, accompanying complicated gastrojejunal anastomosis, was surprising in the light of the relatively low mortality after gastrojejunal anastomosis employing the closed technique in man.

On looking into the literature, it was observed that Martzloff and his associates[2] found that leakage was present in 7 to 10 per cent of the end-to-end small bowel anastomosis made with silk in the dog, using their modification of a closed technique. Similarly executed procedures utilizing a running catgut stitch developed leakage in 25 per cent of the cases. In the Mann-Williamson operation, known as "duodenal drainage" the duodenum, severed from the pylorus and jejunum but receiving all biliary and pancreatic secretions, is anastomosed to the lower small intestine and continuity of the intestine is re-established by gastrojejunostomy. Markowitz[3] states that performance of this operation in dogs with a mortality of 20 per cent indicates a mastery of the technique of intestinal anastomosis. Such a figure is hardly acceptable for even the more complicated intestinal procedures in man.

Intestinal surgery is more difficult in the dog because the lumen is smaller and the gut wall thicker and more friable. Too, attempts at avoiding leakage by broad approximation of a cuff about an anastomosis readily leads to stenosis or obliteration of the lumen by the diaphragm produced. In our experience, we have found that the importance of all of these factors is pyramided by the relatively decreased resistance of dogs to peritoneal insults.

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No comprehensive bacteriologic investigations have been made of cultures obtained from mucosal surfaces about either the closed, aseptic type or open anastomoses. The regular diet fed our animals remained in their stomachs often for prolonged periods so that occasionally, despite precautionary measures, an alimentary residue with its bacterial content augmented contamination at the operative site.

Frequently dogs would succumb to a generalized peritonitis thirty-six to forty-eight hours after establishment of an anastomosis which seemed quite satisfactory from every point of view at completion of the operation. This experience was discouraging, to say the least. A careful study of peritonitis leads one not into its treatment but toward its prevention. Fortunately, in the majority of the cases of peritonitis following gastrointestinal surgery, there is an interval between the onset and an irreversible stage. This period varies with different circumstances; i.e., the amount of contamination and duration of its activity, virulence of the bacterial organisms, resistance of the host, and other less well-known factors. Consistently successful operations required interruption of this cycle by thwarting such potential infection. Chemotherapy appeared to offer this means. Garlock and Seeley[6] had pointed out the value of giving 0.8 per cent sulfanilamide as an isotonic solution subcutaneously in the prophylaxis of peritonitis after colonic surgery. Every eight hours 500 c.c. of 0.8 per cent sulfanilamide solution was given subcutaneously to four dogs upon which a type of duodenal drainage operation had been performed. Three of these animals died of generalized peritonitis. This method of administering the sulfanilamide apparently gave the animals but slight protection. Having in mind the nice results obtained by Jensen and his associates[7] with the local implantation of crystalline sulfanilamide in compound fractures, it was, therefore, proposed to place the drug about the suture lines at the time of operation. This represented the sole modification of our former technique. Results were even better than had been anticipated, for a series of thirty-seven operations were performed without a death from peritonitis. The experience gained with local implantation of sulfanilamide about the suture lines in gastrointestinal anastomoses of varying complexity constitutes the subject of this paper.

METHOD AND MATERIALS

Young adult mongrel dogs weighing between 15 and 25 kg. were secured and fed well for several days prior to operation. All animals were prepared during the twenty-four-hour period before surgery. One pound of raw hamburger or horse meat and water were allowed the night before the operation, but all other food was withheld from the diet. This plan usually provided a collapsed stomach and upper intestinal tract free of partially digested material, thereby lessening the danger from accidental spillage of contaminated intestinal contents

during an anastomotic procedure. Operations were executed with surgical asepsis under ether anesthesia. The skin was shaved, cleansed with soap and water, and prepared with Novak's solution.[8] The operator and assistants wore caps, masks, sterile gowns, and rubber gloves. Interrupted fine silk sutures* were employed almost exclusively in construction of a closed type of anastomosis made according to the Wangensteen[9] technique. After completion of the operation suture lines were carefully inspected, and just prior to closure of the abdominal wall and peritoneum, crystalline sulfanilamide was dusted liberally about the anastomosis, the total amount not exceeding 5 Gm. Adequate parenteral fluids of normal saline solution were administered for the following three days. Liquids were allowed first sparingly after this period, and solid foods were added to the diet on the eighth postoperative day.

RESULTS

The results following adoption of this plan have been summarized in Table I.

There were two deaths from pneumonia on the first and seventeenth postoperative days and one from gastroenteritis on the fourteenth day in this series. At post-mortem in each instance an unusually heavy deposit of fibrin firmly sealed the serosal surfaces at every suture line. Elsewhere the peritoneum was smooth and glistening. With a mechanism for inhibiting bacterial growth locally, normal post-operative healing promptly took place. The rapidity of this process was strikingly apparent in the dog dying during the first twenty-four hours from a regurgitation pneumonia. In animals dying at this interval of generalized peritonitis, there is little fibrin sealing the anastomotic sites and the stitch holes themselves leak contamination.

Markowitz,[4] quoting Saint, suggests that end-to-end anastomosis of the esophagus is difficult and often meets with failure because of the poor blood supply, the constant movement to which it is subjected, the encroachment on mediastinal structures and danger of infections spreading into fascial planes, and absence of serosa or a greater omentum with which to seal anastomotic lines. In the hands of an experienced operator, employing a specialized technique and with preliminary phrenicotomy, the mortality is said to approximate 20 per cent.[5] Reâ[10] and Dragstedt and Mullenix[11] noted a high incidence of fatal mediastinitis after single-stage esophagostomy. On a similar basis clinical experience favors the two-stage procedure for esophageal diverticula. This operation, therefore, seemed to offer a very fundamental test of the ability of the drug to allow a fibrin seal to develop about anastomotic lines, despite bacterial contamination. Three end-to-end anastomoses were made at the level of the cervical esophagus and two anastomoses completed at the end of the esophagus to the duodenum without

*Individual Champion No. 1 silk sutures are threaded on Anchor brand, stainless steel, round-point No. 1 eye needles.

TABLE I

OPERATIVE PROCEDURES COUPLED WITH LOCAL IMPLANTATION OF CRYSTALLINE SULFANILAMIDE (5 GM. OR LESS) ABOUT ALL SUTURE LINES AND COMPARABLE OPERATIONS COMPLETED WITHOUT SULFANILAMIDE

PROCEDURE	SULFANILAMIDE IMPLANTED DEATHS			SULFANILAMIDE NOT IMPLANTED DEATHS		
	NO. OF DOGS	PERITONITIS	OTHER CAUSES	NO. OF DOGS	PERITONITIS	OTHER CAUSES
Heidenhain gastric pouches	9	0	0	39	10	14
Pavlov pouches	2	0	0	41	13	16
Antral exclusion (or resection) and gastrojejunostomy (side-to-side)	2	0	0	16	3	0
Pyloric gastrojejunostomy (end-to-side)	7	0	0	14†	2	2
Gastroduodenostomy (side-to-side)	6	0	1	5	2	0
Jejunal resection and jejunojejunostomy (side-to-side)	1	0	0			
Esophagoduodenostomy (end-to-side) total gastric pouch or total gastrectomy	2	0	0			
Resection with end-to-end anastomosis of cervical esophagus	3	0	0			
Pyloric gastroileostomy (end-to-side) Coloduodenostomy (side-to-side) Ileocolostomy (side-to-side)*	3	0	1			
Ileocolostomy (side-to-side) Pyloric gastroileostomy (end-to-side) Coloduodenostomy (side-to-side)*	1	0	0			
Subtotal gastric pouches	1	0	1			
Jejunojejunostomy (side-to-side) and gastrojejunostomy (side-to side)				17	8	7
				16	6	5
Totals	37	0	3	148	44	44

*In this operation the ileocecal valve is interposed isoperistaltically between the pylorus and the duodenum to reduce the intragastric reflux of bile and pancreatic juice after the manner of Dragstedt's mechanical valve.

†Gastrojejunostomy (side-to-side).

a failure or death. All of these were performed with the clamp or closed method and crystalline sulfanilamide was deposited about the suture line.

In three animals there was a single-stage interposition of the ileocecal valve between the pylorus and duodenum to reduce regurgitation of alkaline intestinal juices after the manner of Dragstedt's mechanical valve. This operation entails a gastroileostomy, coloduodenostomy, and ileocolostomy. One death occurred in this group on the seventeenth postoperative day from pneumonia. At autopsy the peritoneal surfaces were smooth and glistening, and all suture lines were sealed by an organized deposit of fibrin.

DETERMINATION OF SULFANILAMIDE BLOOD LEVELS

Blood levels, employing the method of Bratten and Marshall,[13] for sulfanilamide implanted intraperitoneally or injected subcutaneously in isotonic solution, were determined in a group of control dogs not in the operated series of Table I. Samples were obtained in duplicate each fifteen minutes for the first hour and hourly for twenty-four to thirty-six hours thereafter.

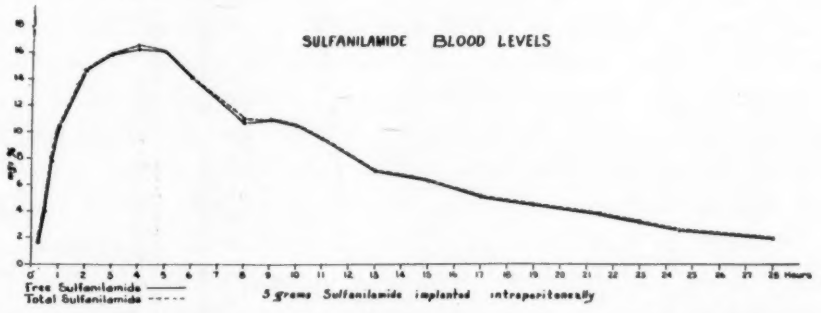

Fig. 1.—There is a prompt rise in the blood level of sulfanilamide, reaching a maximum value in three hours, sustained but a short while, and elimination is nearly complete in twenty-four hours. The values for free and total sulfanilamide check closely since dogs do not acetylate this drug.

The values obtained for blood sulfanilamide following the local implantation of the crystalline form of the drug intra-abdominally are lower than those obtained following the subcutaneous administration of a similar amount in an isotonic solution. A reasonable explanation by analogy for the failure of sulfanilamide in solution to protect against peritonitis is noted in the experiments of Jensen and his co-workers. They pointed out that sulfanilamide placed other than at the site of experimentally produced compound fractures was unable to prevent local infection at the fracture site.* Blood levels for sulfanilamide appear to be less important for the production of local bacteriostasis than the actual concentration of the drug at the site of contamination. In the

*The recent work of Hawking[14] supports this viewpoint. Local application of sulfonamides was found to be significantly superior to systemic treatment with these drugs in protecting against *Clostridium welchii* and *Cl. septique*.

case of local implantation this value probably approximates the solubility of the drug in tissue fluid (*circa* 0.8 per cent), or fifty times the ordinary blood level. It was noted during the process of these determinations that dogs tolerate well relatively high blood levels of sulfanilamide and exhibit few of the symptoms manifested clinically. Apathy and anorexia did occur with large doses given by mouth.

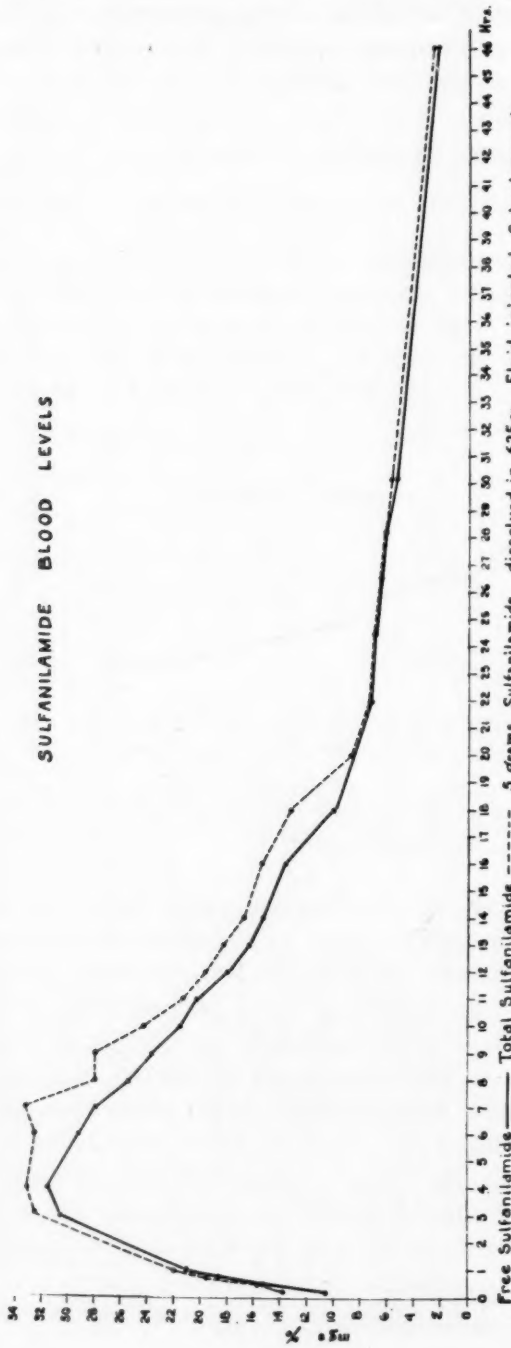
SULFANILAMIDE BLOOD LEVELS
Free Sulfanilamide —— Total Sulfanilamide ------ 5 grams Sulfanilamide dissolved in 625 cc. Fluid injected Subcutaneously
Hrs.

Fig. 2.—The blood levels for sulfanilamide obtained after subcutaneous administration of the drug in 0.8 per cent solution are substantially higher than those noted following intraperitoneal implantation of a similar amount in the crystalline form.

Cyanosis and jaundice were rare. Unlike man, the dog fails to acetylate sulfanilamide circulating in its blood stream so that values for free and total sulfanilamide check closely, and, therefore, the amount available from a single dose may be even 20 per cent more than man would utilize from the same amount of the drug. In addition, recalling the great disparity of weight between man and dog, the canine tolerance appears even more manifest. In man acetylation is a detoxification process, a probable further indication of a decreased tolerance as contrasted with dogs.

Clinical application of this work has been cautiously expanded since so little is known of man's ability to assimilate safely the sulfanilamide so rapidly absorbed following its implantation intra-abdominally in the crystalline form. In this respect, Watson and Spink[12] have pointed out that mild liver damage secondary to toxic drainage from intraperitoneal sepsis via the portal circulation can be converted into outspoken hepatic dysfunction characterized by urobilinogenuria, elevation of serum bilirubin, and jaundice by the administration of therapeutic doses of sulfanilamide.*

In instances of operation for colonic resection with primary anastomosis at the University of Minnesota Hospitals, usually 2 or 3 Gm. of sulfanilamide† are implanted about the suture lines, and an additional 1 Gm. is distributed over the wound edges of the abdominal wall above the peritoneum during closure. The use of sulfanilamide has been limited in gastric resections to those cases with perforation onto an adjacent viscus; i.e., a pancreas into which a contaminated site must be opened.

The efficacy of implanting crystalline sulfanilamide about colonic anastomosis in man on the indications stated above has been difficult to evaluate. The adoption of the closed method of anastomosis has made resection with primary anastomosis, wherever feasible, the method of choice in surgery of the colon. Large, fixed lesions have been removed under trying circumstances and anastomosis made with surprisingly low operative risk. The risk of primary colon resections from the University Hospital experience would appear to be about 5 per cent. If sulfanilamide could be embedded in a vehicle which would permit gradual liberation of the drug over a prolonged period, the bacteriostatic effect of local implantation would be enhanced greatly. Whether the local implantation of sulfanilamide will make such anastomosis even safer remains to be determined. Mindful of the great protective value of the method in the dog in preventing the lysis of fibrin and in encouraging early agglutination of the approximated serosal surfaces, it

*Investigation is now in progress on a method of combining the sulfanilamide with a vehicle so as to maintain a prolonged local action and to produce a delayed rate of absorption into the circulation.

†Sulfathiazole has been used more often recently.

is reasonable to believe that local implantation of crystalline sulfanilamide or allied chemotherapeutic agents may prove a worth-while adjunct to the closed anastomosis in man.

Experimentally the local implantation of crystalline sulfanilamide about gastrointestinal suture lines in dogs appears to promote healing by inducing local bacteriostasis and inhibition of fibrinolysis. This mechanism is an aid in preventing peritonitis. Clinical evaluation of its worth requires additional trial.

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PERITONEAL VACCINATION, IRRIGATION, AND CHEMOTHERAPY IN THE TREATMENT OF EXPERIMENTAL PERITONITIS

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IN THE PAST much of the experimental and clinical work of peritonitis has been concerned with its prevention during accompanying gastrointestinal disease and gastrointestinal surgery or with the treatment of altered physiologic functions that arise during the disease. The epochal contributions toward a better understanding of distention, shock, and fluid requirements of this disease have done much to reduce the mortality. Nevertheless, therapeutic measures combating the etiological bacteria of this disease should always receive first consideration.

Bacterial peritonitis is usually due to perforation secondary to other disease of the gastrointestinal tract. The resulting bacterial flora is accordingly diverse. Altemeier[1] in an extensive review and from personal observations and similarly Bowers and associates[2] and Meleney and co-workers[3] have emphasized this diverse bacterial flora. Altemeier also concluded from his studies that it was impossible to predict the course of appendical peritonitis from the kind of bacteria isolated in any one case, but that those patients with only a single bacterial type of culture usually survive the disease.

Bacteriologic studies were done at the time of death on the peritoneal exudates of 15 dogs by means of direct smears and aerobic and anaerobic cultures, with complete identification of the organisms. In 4 dogs with cecal perforation, direct smears showed gram-negative bacilli, streptococci, gram-positive spore formers, and very few diphtheroids. Aerobic cultures showed *Bacillus coli* and *Streptococcus viridans* (enterococcus). Anaerobic cultures showed the above organisms plus *B. welchii.*

In the 11 dogs with ileal perforation, gram stain showed numerous small gram-negative bacilli, many gram-positive spore formers, streptococci and occasional gram-positive diplococci. Aerobic cultures showed in all instances *B. coli* and *Str. viridans.* In 3 of the 11 cases cultures also showed *Staphylococcus albus, B. proteus, B. aerogenes,* and a gram-negative motile bacillus of the Salmonella group. Occasionally diphtheroids and mucoid variants of *B. coli communis* were cultured. Anaerobic cultures showed *B. welchii* plus the above organisms.

*Bacteriological work done by Dr. Edward Birge, of the Wisconsin State Laboratory of Hygiene.

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These studies would tend to demonstrate that the same flora of organisms exists in the peritoneal cavity as is normally present in the lower ileum and cecum. Of interest was the observation that there was a marked paucity of organisms in the smears made from exudates of cecal perforation as compared to those made from exudates of ileal perforation.

In our experimental work we hoped first to determine the effectiveness of peritoneal vaccination toward subsequent peritonitis, and second to determine the therapeutic efficacy of peritoneal irrigations and chemotherapy in peritonitis. All this work was done upon dogs weighing more than 7.5 kg. No dog had any previous abdominal surgery and all operative procedures were done under open-drop ether anesthesia with morphine sulfate 1½ to 2 gr. two hours before operation.

In order to obtain a control series, we first attempted the production of perforating lesions in the cecal pouch of dogs. In 6 dogs the arterial supply to the cecal area was ligated and 3 dogs died. In 5 dogs, in addition to the arterial ligation, the corresponding cecum was crushed with hemostats for ten to thirteen minutes. Two of these dogs died. In 5 dogs a 1 cm. opening was made into the cecum and only 1 of these dogs died. It is seen that none of these procedures carried a mortality of over 50 per cent.

In an endeavor to increase this mortality, virulent *B. coli* (750 million per kilogram), obtained from a fatal case of peritonitis in a dog, were given intraperitoneally in saline solution to 3 dogs, and all lived; and in a 2 per per gum tragacanth suspension to 4 dogs and again all lived. One billion *B. coli* (No. 300 from Dr. B. Steinberg) (per kilogram) suspended in gum tragacanth given intraperitoneally in 6 dogs produced death in all cases in thirty-six hours.

To obtain a more diverse bacterial flora in peritonitis, we followed the methods of Okada[4] and of Bergh, Bowers, and Wangensteen[5] and made a 1 cm. opening in the ileum 8 cm. from the ileocecal junction. Of 15 dogs, 14 died, a mortality of 93.33 per cent. Ten dogs died of generalized peritonitis within forty-eight hours, and autopsy demonstrated the presence of a serosanguineous exudate and no adhesions. Three dogs died between seventy-two and ninety-six hours after surgery, and necropsy revealed numerous adhesions and occasional small abscesses. One dog survived three weeks and died after the apparent intraperitoneal rupture of a large abscess. The surviving dog on later exploration demonstrated a complete closure of the ileal perforation by adhesions to adjacent loops of bowel and omentum. This group of fifteen dogs served as our main control series.

Peritoneal vaccination, a prophylactic procedure against peritonitis according to the work of Steinberg and Goldblatt,[6, 7] has been used when peritoneal contamination is likely to occur during or after gastrointestinal surgery. The commonly used antigen is coli bactragen,* a

*Made available through the courtesy of Dr. B. Steinberg.

suspension of formalized colon bacilli in gum tragacanth and aleuronat. This agent increases the local peritoneal resistance and its action is nonspecific, for the protection is not limited solely to *B. coli*, but it also affords protection against other bacilli. Other agents have been used but apparently this colon bacillus suspension is the most effective one.[8]

In 6 dogs 7.5 to 20 c.c. of coli bactragen, depending on the size of the dog (1 to 1.5 c.c. per kilogram), was injected intraperitoneally prior to opening the distal ileum. Six dogs were used, of which 2 were injected twenty-four hours, 2 forty-eight hours, and 2 seventy-two hours before the operation. All dogs lived. Laparotomy a month later showed many fibrous peritoneal adhesions and a scar at the site of the ileal opening 0.5 to 0.75 cm. in length.

In further work coli bactragen was injected intraperitoneally in 6 dogs six hours before opening the ileum. Two of these dogs died and necropsy revealed a generalized peritonitis with many adhesions and a partial closure of the ileal opening. The surviving dogs on exploratory laparotomy three months postoperatively showed numerous fibrous peritoneal adhesions and a scar at the site of the ileal opening.

In 3 dogs coli bactragen was injected at the time the ileum was opened and all dogs died within forty-eight hours. Autopsy revealed a sanguineous exudate, a few fine adhesions, but no attempt at closure of ileal opening.

Coli bactragen was then given intraperitoneally to 5 dogs, 1 of which was injected simultaneously with one billion *B. coli* in 2 per cent gum tragacanth per kilogram of body weight; 2 were injected with *B. coli* in twenty-four hours and 2 forty-eight hours after the administration of Coli bactragen. The first dog died and all the others survived. At autopsy a large amount of serosanguineous exudate was present in the peritoneal cavity and there were only a few adhesions. Exploratory laparotomy on the other dogs showed no adhesions and peritoneal surfaces were smooth and glistening.

Peritoneal irrigation in the treatment or prophylaxis of peritonitis is one of the older therapeutic procedures. French and German surgeons often wash out the peritoneal cavity with liberal amounts of water or saline solution before closure of each laparotomy as a prophylactic measure and also use this as a therapeutic procedure. Tauc and Trzebicky[9] employed antiseptic solutions as peritoneal irrigants and noted some improvement over controls. One of the most recent reports, that of Behan,[10] speaks favorably of alcohol peritoneal lavage at time of surgery in the presence of peritonitis. In our work saline sodium ricinoleate (soricin) and zephiran* were used. In 2 dogs immediately following ileal perforation 10,000 c.c. of normal saline solution as a continuous peritoneal irrigation was used and both dogs died. At autopsy no adhesions were found and peritoneal fluid was markedly hemorrhagic.

*Material made available through the courtesy of Alba Pharmaceutical Company.

In 4 dogs zephiran (alkyl-dimethyl-benzol ammonium chloride) irrigations were employed. In 2 dogs immediately following ileal perforation 5 liters of a 1:10,000 solution were used and both dogs died within thirty hours. Two other dogs were irrigated with a 1:20,000 solution with similar results. Autopsy findings were the same as with saline irrigations. In 4 dogs 20 c.c. of 1 per cent sodium ricinoleate solution (soricin*) as a sclerosing solution was placed into the peritoneal cavity after ileal perforations. All dogs died within seventy-two hours. At necropsy some adhesions were present, but the ileal perforations were not closed.

Neoprontosil was chosen as a chemotherapeutic agent in most of our work because of its ease of administration. Bowers, Burns, and Mengle[11] reported beneficial effects with prontosil in spreading peritonitis in dogs; and Cooper, Gross, and Lewis[12] felt that sulfanilamide was of value in *B. coli* and *B. proteus* peritonitis in mice, but they noted no effect with *B. pyocyaneus* peritoneal infections. As a prophylactic measure Garlock and Seeley[13] in a preliminary report felt that it decreased their incidence of peritonitis following intestinal resections and they were impressed by the smooth uncomplicated convalescence of their patients.

Neoprontosil was given to 16 dogs immediately after the ileum was opened. Therapy consisted of intramuscular injection of 7.5 c.c. q.i.d. the first day, 7.5 c.c. t.i.d. the second to fourth days, and 7.5 c.c. b.i.d. on the fifth and sixth days. Four dogs died, a mortality of 25 per cent. Autopsy upon these revealed definite attempts at closure of the perforation in all cases. Only a small amount of peritoneal fluid was present. Exploratory laparotomy upon the 12 surviving dogs five to seven weeks postoperatively revealed a minimal number of fine adhesions in 4 dogs, a moderate number in 3 dogs, and dense adhesions in 5 dogs. In 3 of the 12 living dogs blood samples on the third day showed only a trace of the drug.

In addition, blood sulfanilamide determinations were carried out on 5 more dogs. These dogs received the same dosage of sulfanilamide as did those in the preceding experiment. Two dogs were used as controls and 3 had openings made in the ileum. Blood specimens were taken one hour and three hours after the second injection each day and in every case only a trace of sulfanilamide was found. The peritoneal exudate obtained from one of the dogs with ileal perforation on the first postoperative day showed 1.8 mg. per cent sulfanilamide. A second dog with ileal perforation was sacrificed on the second postoperative day and the peritoneal exudate showed a trace of sulfanilamide. The third dog with ileal perforation was explored on the

*Material made available through the courtesy of Merrill Company.

third postoperative day and no peritoneal exudate was found. The serosa was smooth, injected, and the ileal opening was covered by omentum.

Neoprontosil was then given to 4 dogs, with the first injection given four hours after the operation. One dog died, a mortality of 25 per cent. Autopsy revealed extensive fibrinous adhesions and very little exudate. Subsequent exploratory laparotomy on the 3 living dogs revealed minimal fibrous adhesions in 1 and dense adhesions in 2. On the third day blood samples from the dogs that survived showed only a trace of neoprontosil during the period of treatment.

In 6 dogs neoprontosil was begun eight hours after the ileum was opened and 50 per cent of this group died. Post-mortem findings were the same as in the immediately preceding fatal group. One of the surviving dogs was sacrificed on the fourth day and only a trace of neoprontosil was found in 10 c.c. of viscid purulent peritoneal fluid. The ileal opening was closed and there were extensive peritoneal adhesions. Blood samples in the surviving dogs again showed only a trace of neoprontosil.

Five dogs were then given the initial dose of neoprontosil sixteen hours after the operation. Three dogs died within thirty-six hours. Autopsy revealed a large amount of sanguineous fluid and few fibrinous adhesions. Two dogs died seventy-two hours postoperatively and autopsy showed very little exudate but numerous adhesions.

Three dogs were treated solely by inserting 3 to 5 Gm. of sulfanilamide powder into the peritoneal cavity at the time the ileum was perforated. Two of these dogs died, a mortality of 66.66 per cent. Death occurred seventy-two hours postoperatively and autopsy showed many adhesions and a moderate amount of pus.

A solution of 0.5 per cent sulfanilamide was introduced intraperitoneally in 4 dogs at the time the ileum was perforated. Two of the dogs were given 250 c.c. of the solution; the remaining 2, 500 c.c. All dogs died within forty-eight hours and showed at autopsy a large amount of sanguineous peritoneal fluid and few adhesions.

Promine* was the last chemotherapeutic agent tried. A 1 cm. opening was made in the ileum in 8 dogs and 1 Gm. promine injected intravenously at the conclusion of the operation. The subsequent injections of 1 Gm. promine were given intramuscularly as follows: t.i.d. the same day, t.i.d. the second to fourth days, and b.i.d. the fifth and sixth days. Of this group, 75 per cent survived. Necropsy findings on the 2 fatalities showed partial closure of the ileal opening, 50 c.c. and 200 c.c. of pus, and marked adhesions. Exploratory laparotomy on the surviving dogs revealed minimal adhesions in 2, moderate adhesions in 1, and marked adhesions in 3.

*Experimental material made available through the courtesy of Parke-Davis and Company.

DISCUSSION

In our work we were able in a small group of dogs to confirm the work of Schmidt and Taylor[14] and Bergh, Bowers, and Wangensteen[5] that it is practically impossible to obtain a mortality of over 50 per cent in peritonitis induced by perforation or gangrene of the cecum. However, perforation of the distal ileum as reported by the latter workers produced a 100 per cent mortality, and our experience closely approached this with 93.33 per cent fatality. This method brings about a peritonitis with a diverse bacterial flora such as is seen in human beings following gastrointestinal perforation. The high mortality rate provides a basis for the estimation of therapeutic or prophylactic procedures.

Peritoneal vaccination (with coli bactragen) in dogs prior to the operative production of ileal perforation protects against subsequent peritonitis. Apparently it should be given twenty-four to seventy-two hours before the operative procedure. This protection agrees with the result of other workers.[15, 16, 17] The vaccine produces a sterile peritoneal exudate rich in phagocytes which combats an infection in its early stages and subjugates it before an overwhelming bacterial growth occurs. Local tissue changes, such as edema and congestion, also prevent marked bacterial tissue invasion. The inflammatory defensive mechanism is a stage ahead of the bacterial offense following vaccination.

It appears that peritoneal irrigations have no value either mechanically or chemically in the treatment or prevention of peritonitis. The peritoneal washings do not reach all surfaces and remove protective agents in the exudate as well as any bacteria or their toxins. Those bacteria or bacterial toxins that have invaded tissues or lymphatic and hematogenous channels are not reached by the irrigations. We also know from some previous work in our laboratory that continuous peritoneal lavage is shocking and often results in death, even in an unaffected peritoneal cavity.

Sulfanilamide, neoprontosil, promine, and related drugs have been shown[18, 19] to be bacteriostatic and thereby permit the physiologic immunity reactions to combat the invading bacteria. The drugs are most effective against certain hemolytic streptococci, *B. coli,*[12] and *B. welchii;* the last two organisms are most common in any case of peritonitis following gastrointestinal perforation. As is generally agreed and as shown in our work, the earlier in the course of an infection the drug is given the better are the results. The low level of blood sulfanilamide in our dogs suggests that the drug is rapidly excreted and that a larger number of injections may be even more effective.

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THE LOCAL USE OF SULFANILAMIDE

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INTRODUCTION

THE subject of the application of sulfanilamide crystals to wounds of the body made by trauma or by the surgeon is a subject which is growing in importance, particularly with the vast number of casualties that are appearing in the present war as well as the increasing number of auto accidents. This method is becoming more common in use throughout the world and seems to be a timely one for discussion at this moment. Sulfanilamide is used because it is more soluble than sulfapyridine or sulfathiazol. Its concentration in the blood shows that it is picked up more rapidly than the other two of this group.

HISTORY

The first material was published by Jensen and co-workers in SURGERY in 1939. Our attention was directed to it by Key[2] in November, 1939, at Memphis, during a meeting of the Southern Medical Association. These authors had made a study of its use in compound fractures after thorough débridement. They did quite an extensive amount of experimental work on rabbits and other animals and found very little, if any, delay in union from the use of this crystalline material in and around the site of the fracture. It was used both with and without the oral administration of the drug with good results. No infections were encountered in their cases. Russell and Falconer[4] (1940) showed that the local application to the rabbit's brain does not cause any appreciable damage to the tissue. However, due to the brain's being encased in a solid vault, there was some mechanical disturbance and it was advised to use the solution if possible. Colebrook[5] (1940) called attention to the experiment done by Legroux of Paris, in the Academy of Surgery. This experiment was carried out on guinea pigs. The abductor muscle was crushed and a small piece of gauze with *Streptococcus hemolyticus* and B. C. Welchii gas *bacillus* organism was inserted. The gas bacillus is amenable to the sulfanilamide but not so susceptible as the streptococcus. The control pigs died in from two to three days. Those in which the wound was dusted with sulfanilamide powder before closure died in from four to seven days, but, if the wound was opened on the second day and the infected gauze removed and the wound dusted with sulfanilamide, they recovered without débridement. During the present war the English and French surgeons in France and Belgium were instructed to give the wounded patients 2 Gm. of sulfanilamide by mouth

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and the wounds were impregnated with sulfanilamide crystals when first seen. The patients were then sent back to the field or base hospital, and a thorough débridement was done, the wound being redusted with powder many hours later. The final treatment carried out was irrigation, débridement, packing with sulfanilamide powder, and immobilization of the part. It is known that the powder is soluble in serum and penetrates the fissures of the wound and ragged edges to a great extent. An air pump with a flask and a sterile tip of glass was used to force the powder into the crevices of the laceration. The powder acts in the serum as well as by absorption into the blood stream and lymphatics. Varying lengths and sizes of crayons compressed of the powder and containing 20 Gm., were used, being pushed into bullet wounds. The absorption is much slower in this method. Collapsible tubes of the emulsion of sulfanilamide are being used at the present time in France. The question has arisen of the sterility of the powder. It first was autoclaved, which, it was found, broke it up into its chemical components, often dissolving it into a brown liquid. Since then it has been used in stock bottles which are sterilized by the heat flame or alcohol on the outside and into which it is poured, just as sterile saline solutions are into sterile containers for handling and for use in the surgical team. One of us (J. G. D.)[6] has called attention to the use of the powder as an adjunct in the treatment of peritonitis and the other (L. W. L.),[7] to the use of the powder as an aid in the treatment of breast resections, appendical and pelvic abscesses, pyelitis complicating surgical diseases of the abdomen, and local infections, lacerations, and compound fractures and injuries.

USES

The typical use of sulfanilamide crystals is divided into office and hospital use.

Office Use.—The types of cases treated in the office are those of local infections, small lacerations, boils and abscesses, and the lesser types of injuries in which powder is placed in the wound and sewed up without drainage. If the infection and injury seem to be serious enough, sulfanilamide is given by mouth in addition to the local use. Where the ointment is indicated in office treatments, we use equal parts of sulfanilamide crystals and lanolin thoroughly mixed, preferring the anhydrous type of sulfanilamide ointment because it seems to be more readily absorbable than that placed in petrolatum.

Hospital Use.—Hospital treatment consists of: (1) *Crushing and lacerated injuries,* in which the wound is thoroughly débrided, after scrubbing, and preparation of the area, and dusted with sulfanilamide powder, being closed without drainage. (2) *Compound fractures,* in which the patient is treated for shock, after which there is thorough preparation of the injured part with soap and quantities of sterile water, débridement, apposition of the fractured extremity, and, if the fractures

cannot be aligned and held properly in place, the placing of vitallium metal screws and plates into the bone to hold the fractures in situ. Sulfanilamide powder, 20 Gm. for adults and proportionally smaller amount for children, is placed into the fracture site both beneath and on top of the periosteum and the subcutaneous area. The wound is closed without drainage and a plaster of Paris splint applied to immobilize the part. It is interesting to note here that we have had some mental worry in some of these cases of compound fractures due to a temperature rise on the third and fourth days which would progressively go higher each day. All of these patients were receiving sulfanilamide by mouth and on discontinuance the temperature subsided to normal. (3) *Carbuncles,* the treatment of which has been satisfactory in our hands by the use of intravenous anesthesia, thorough incision with the radioknife, removal

TABLE I

ABSORPTION FROM DENUDED AREA FOLLOWING RADICAL RESECTION OF BREAST (30 GM. SULFANILAMIDE POWDER)

1st postoperative day	6.3 mg.*
2nd postoperative day	7.8 mg.
3rd postoperative day	9.7 mg.
4th postoperative day	3.1 mg.
5th postoperative day	0.88 mg.
6th postoperative day	0.06 mg.
7th postoperative day	None available

*In Tables I-V, rate as shown is in milligrams per 100 c.c. of blood serum.

of the infected tissue by electrocoagulation, and packing with sulfanilamide powder. Freedom from pain and sepsis following this procedure has been the rule. (4) *Local abscesses,* treatment of which with incision and drainage and daily applications of sulfanilamide powder dusted into the cavity has shortened the duration of the infection and apparently aided materially in the cure. We have noted breast cases referred to us for radical resection in which biopsies had been made in other small hospitals in which there was infection from previous surgery with marked induration around the carcinomatous breast from incision and not from the malignancy. These cases have been handled satisfactorily by the use of 20 Gm. of sulfanilamide powder; in one case as much as 30 Gm. were dusted into the wound before closure of the skin flap. These cases

TABLE II

ABSORPTION FROM NORMAL PERITONEUM WITH NO PERITONITIS (15 GM. SULFANILAMIDE POWDER)

1st postoperative day	12.5 mg.
2nd postoperative day	9.7 mg.
3rd postoperative day	7.8 mg.
4th postoperative day	3.1 mg.
5th postoperative day	0.88 mg.
6th postoperative day	0.5 mg.
7th postoperative day	None; all pus and symptoms of pyelitis clearing up

have progressed satisfactorily without infection and the large raw area has offered great absorbent powers as will be shown in Tables I-V on the rate of absorption. One patient with frank acute appendicitis with bilateral pyelitis complicating the disease had 20 Gm. of sulfanilamide powder placed in the peritoneal cavity which cured her pyelitis without further administration of the drug. (5) *Appendical and pelvic abscesses,* which have been treated most successfully without drainage by incising and irrigating the abscessed cavity, placing 20 to 30 Gm. of sulfanilamide powder into the abscess, and closing the abdomen without drain-

TABLE III

APPENDICAL ABSCESS (15 GM. SULFANILAMIDE POWDER)

1st postoperative day	1.9 mg.
2nd postoperative day	1.4 mg.
3rd postoperative day	0.51 mg.
4th postoperative day	0.41 mg.
5th postoperative day	0.09 mg.
6th postoperative day	0.03 mg.
7th postoperative day	Negative; patient discharged from the hospital

age. The rate of absorption from such walled-off cavities is much slower than in fresh denuded areas or in the peritoneum itself. (6) *Peritonitis,* which locally following acute appendicitis has been treated successfully without any deaths by dusting the sulfanilamide powder into the peritoneal cavity, and which generally has been treated with sulfanilamide in the peritoneal cavity with drainage with marked success. One of us (J. G. D.)[6] reported 1 death in twenty-five cases of perforated appendicitis with peritonitis in which this drug was used. Since that time

TABLE IV

GENERAL PERITONITIS (15 GM. SULFANILAMIDE POWDER)

1st postoperative day	15.0 mg.
2nd postoperative day	10.0 mg.
3rd postoperative day	6.0 mg.
4th postoperative day	4.0 mg.
5th postoperative day	1.88 mg.
6th postoperative day	0.88 mg.

twenty-six additional cases have been added without any deaths. It is definitely known that the absorbability of the drug is proportional to the peritoneal reaction that is present. (7) *Prophylactic Use in Abdominal and pelvic surgery,* in which all cases of chronic salpingitis, hydro-

TABLE V

CHRONIC PYOSALPINX (15 GM. SULFANILAMIDE POWDER)

1st postoperative day	4.5 mg.
2nd postoperative day	1.55 mg.
3rd postoperative day	0.61 mg.
4th postoperative day	0.06 mg.

salpinx, supravaginal hysterectomy, and tubo-ovarian abscess with removal are treated by the use of sulfanilamide powder dusted into the area of the pelvis. The stump of the cervix particularly has been closed with no complications in any cases after its use. Its use is advantageous as a prophylactic measure following any gastrointestinal surgery with soiling of the peritoneum.

RATES OF ABSORPTION

The typical rate of absorption is shown in Tables I-V.

The maximum concentration in any of our cases has been 19.5 per cent. The minimum concentration shown has been 1.9 per cent. The effectiveness of the drug is lost if and when concentration falls below 1 mg. per cent. In our opinion the ideal concentration desired is from 6 to 10 mg. per cent.

CONCLUSION

1. Attention is called to the use of sulfanilamide powder locally.
2. The various methods and types of cases aided by it are herein noted.
3. Sufficient concentration in the serum can be obtained in conditions requiring its use.
4. Autoclaving destroys the effectiveness of the drug.
5. Its rate of absorption is dependent upon the vascularity of the area in which it is placed.
6. Attention is directed to its use in war surgery as a prophylactic measure in the field.
7. No complications can be noted in any cases under our care due to the drug.

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SURGERY OF BRAIN TUMORS TODAY AND TEN YEARS AGO*

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TEN years ago I based a paper upon a series of 298 brain tumors which I had removed in the course of twenty years. In the first ten years there were 38; in the second ten years, 260. In the past ten years, the third decade of my work, we have removed 796 brain tumors. We have, therefore, a series of 1,094 brain tumors, removed partially or *in toto,* on which these remarks are based. This material can be studied from many angles. Naturally, in an address such as this, only a few points can be stressed.

In my paper ten years ago I discussed methods of diagnosis and technical methods of tumor removal. Since then, these technical methods have been pretty well standardized and no new methods have been introduced, although we have learned to use more effectively the methods we then had at our disposal, some of which were new at that time. On the diagnostic side there is a constant improvement, though nothing very fundamental has been added. A good deal is being written nowadays about electroencephalography and its relation to diagnosis. About these things I shall have a few words to say later, but for the most part I shall devote my remarks to a different phase of the subject.

For the general practitioner, as well as for the specialist, one point is always of deep interest; namely, the operability of tumors and their malignancy. On this point our series gives valuable information. I have classified the tumors according to the types that we recognize today (Table I).

TABLE I

PATHOLOGIC CLASSIFICATION OF 1,094 BRAIN TUMOR CASES

Meningiomas	178	16.4%
Astrocytomas	124	11.3%
Acoustic neuromas	90	8.2%
Pituitary tumors	70	6.4%
Hemangioblastomas and angiomas	50	4.5%
Craniopharyngiomas (suprasellar cysts)	25	2.2%
Medulloblastomas	67	6.1%
Ependymomas	48	4.3%
Oligodendrogliomas	26	2.3%
Miscellaneous tumors (under 1 per cent)	138	12.6%
Spongioblastomas multiforme and unclassified	207	18.9%
Malignancies, metastatic	71	6.4%

In this table, I have placed those brain tumors most commonly encountered and have placed them in order of their malignancy, beginning with the benign and working down to the most malignant. From this,

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you will see that about 45 per cent of all brain tumors fall into the benign group and that another 6 per cent are semibenign; that is, they are very slow growing and either can be totally removed, or these patients, by repeated operations over a period of years, can be kept comfortable and often are able to follow their occupation even though it be a very strenuous one. Some years ago a patient who was a cowpuncher used to come to me every twelve or eighteen months to have some more tumor removed so that he could carry on (Fig. 1). In this way it was possible to keep him comfortable and working for a number of years.

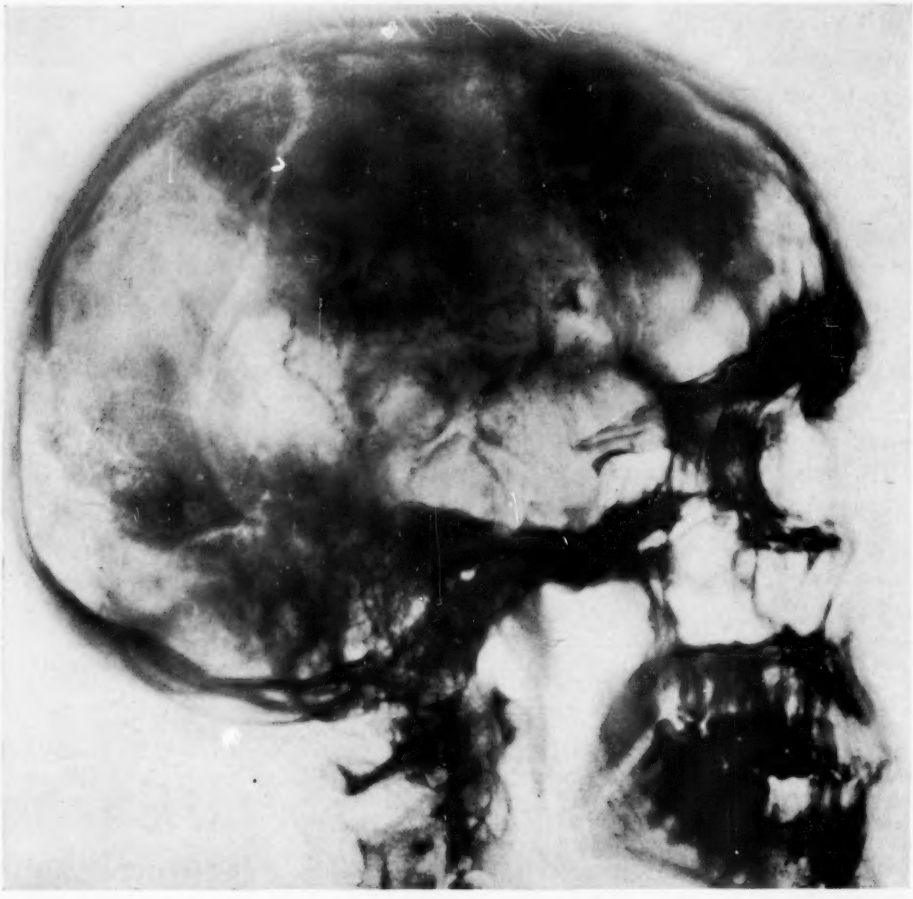

Fig. 1.—X-ray plate of a case of ependymoma. The peculiar fluffy appearance of the calcification is characteristic of this type of tumor.

Meningiomas.—The most favorable type of tumor is the meningioma. It is only in rare instances that these undergo malignant degeneration. They are well encapsulated and can be removed completely. It may be possible to remove them in one mass, but, as they frequently are very large, it is wiser to remove them piecemeal. This is safer though not so spectacular. (Fig. 2.) The sudden removal of a huge tumor—they often weigh several hundred grams—may throw the patient into shock,

while this danger may be completely avoided when it is removed in pieces. Removing a tumor in this fashion necessitates more exacting methods of hemostasis, and this is where electrocoagulation has become indispensable. The removal of these tumors is tedious and time-consuming. Frequently the brain tissue has to be pushed back and great gentleness is necessary in order not to interfere with the function of this brain tissue. Of course, the importance of sparing the surrounding brain tissue depends greatly upon the location of the tumor. Thus, if a tumor is on the left side, near the origin of the sylvian fissure, injury to the speech mechanism is an ever-present danger. It is impossible to be certain during an operation whether the speech center has been permanently injured. For this reason, such operations, in which there is a question

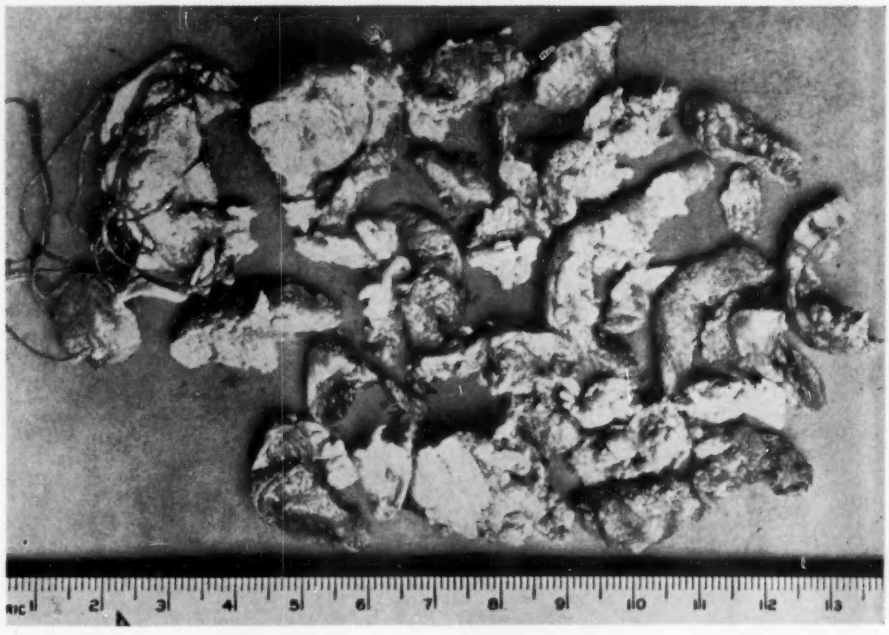

Fig. 2.—Olfactory groove meningioma that was removed piecemeal.

of saving the speech mechanism, are better carried out under local anesthesia. The anesthetist, in talking to the patient, can keep the surgeon informed of any speech disturbance. This information is a great comfort and is of great prognostic value. If, after the tumor has been removed, the patient speaks even an occasional word, the surgeon may be certain that the patient's speech mechanism is intact. At the time the operation is completed, the patient may not be able to speak, due to the edema of the brain which lay adjacent to the tumor, but, thanks to the brief period of speech after the tumor was removed, one is able to assure the family and the patient that speech will return. This is most comforting to both the surgeon and the family. I recently went through such an experience. A woman, 65 years of age, had a meningioma just below her sylvian artery (Fig. 3). Before operation her speech had

been perfect. At the end of the operation she said a few words, and then for over a month she said nothing but "no." Usually speech begins to improve in a week or two and longer delay in recovery is harrowing to both the surgeon and the family. Often it worries the patient greatly and the worry, at least in this case, increased the inhibition which had to be overcome before she started to speak. It was, therefore, very comforting to be able to reassure the relatives that there would be ultimate recovery.

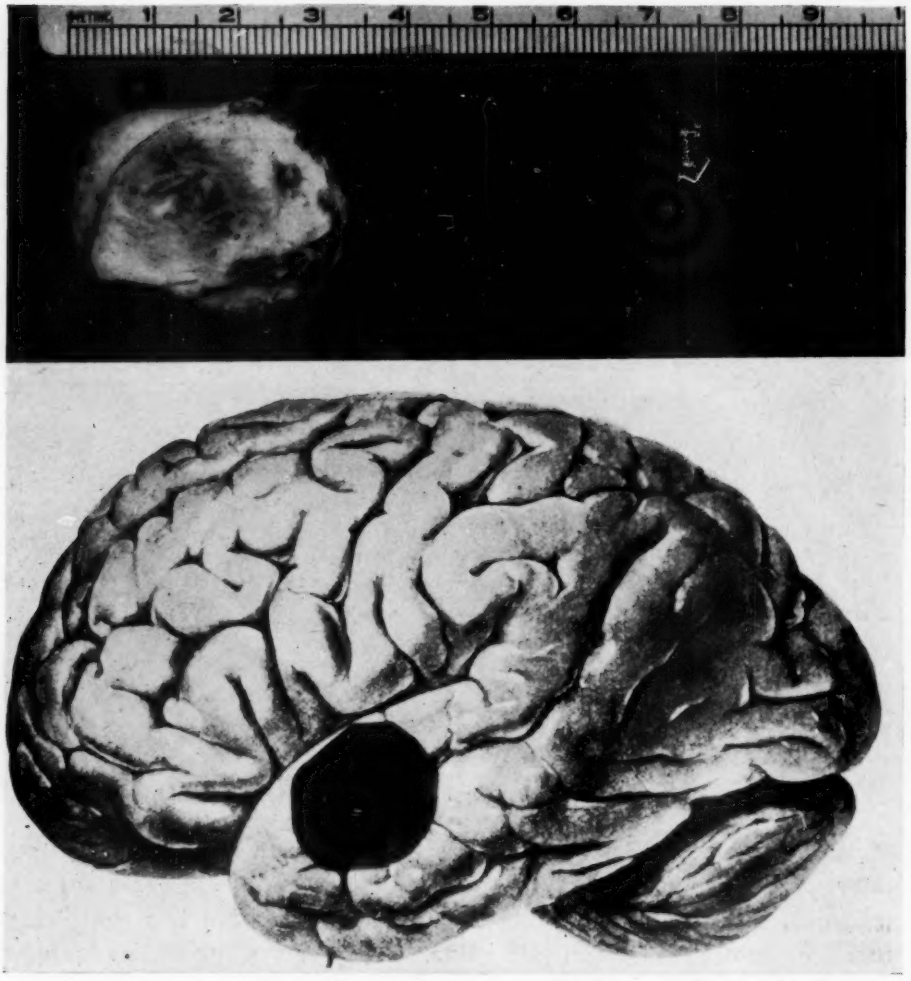

Fig. 3.—Meningioma and its location causing marked speech disturbance from which patient recovered completely.

Cases in which speech may be affected are, however, the only ones that I do under local anesthesia today; all others are done under avertin with the addition of local anesthesia. Ten years ago we still were doing everything under local anesthesia.

In removing any tumor, blood vessels have to be occluded. I had the impression ten years ago that electrocoagulation, which then was a new

procedure for occluding vessels, was preferable to the old silver clips. Our experience since then has confirmed this, and for all vessels that have to be occluded—"tied"—electrocoagulation is used if possible. Occasionally silver clips may be necessary.

The mortality in the removal of meningiomas has steadily gone down. In the 117 cases operated upon in the last ten years, it was 19 per cent; while in the last five years, in 61 cases, it was only 9.8 per cent.

Astrocytomas.—The second most frequent tumors in the benign group are the astrocytomas. Many of these, especially when they occur in the cerebellum, are cystic in character. The results of operation upon these cases are eminently satisfactory. If the cyst is evacuated, all pressure signs recede, but this will not effect a cure. To cure these cases the solid portion, the growing portion spoken of as a nubbin, must be removed; otherwise, sooner or later there will be a recurrence. The cystic fluid in these tumors is secreted either by the solid portion of the tumor or is the result of degeneration; but why some of these tumors, which histologically are indistinguishable from one another, should produce a large amount of fluid and others not, is not at all clear. This is one of a number of instances which suggests that there may be a chemical interaction between tumor cells and normal brain tissue and that different regions of the brain react differently to the same group of cells.

We also lack, thus far, any adequate explanation of the fact that some tumors develop much more frequently in certain regions of the brain than in others.

Acoustic Neuromas.—The third large group consists of the acoustic neuromas, tumors which grow from the eighth nerve itself. In our series there were 89 cases, which places these as the third most common tumor in the benign group. In the last ten years there has been a greater change in the handling of this type than in the treatment of any other type of brain tumor. The first important contribution about them was made twenty years ago by Cushing in his book on *Acoustic Neuromas.* He advocated at that time, in fact believed up to his death, that the best treatment was a partial or, as he termed it, intracapsular removal of these tumors. The operation consisted of a bilateral cerebellar exposure with retraction of the cerebellar lobe on the side of the lesion. The capsule was split and as much of the tumor was removed as the surgeon deemed wise, but most of the capsule was left and sooner or later these patients had a recurrence. Sometimes they were free of symptoms for many years. I have some patients operated upon by that method who have been free of symptoms for many years, one of them for as many as eleven years. Today the operative approach is unilateral and, in order to get enough room, after reducing pressure by a ventricle puncture, part of the lateral lobe of the cerebellum is resected (Figs. 4 and 5). If one is careful not to injure the nuclei of the cerebellum, the resection of the cerebellum does not give rise to any serious symptoms, at most perhaps a transient ataxia. In fact, resecting the cerebellum is less harm-

ful than retracting it for a prolonged time because prolonged retraction injures its blood supply, thus destroying its function; furthermore, leaving traumatized avascular tissue in the wound increases the possibility of an infection. This operation is extremely difficult; in fact, I consider operations for eighth nerve tumors among the most difficult we have to perform. There is no operation in which a skillful assistant is so important. The results, however, are better than by the older method and,

Fig. 4.—Acoustic neuroma and cerebellum that was resected.

though our mortality is still much too high, in the last 20 cases it has been 20 per cent, while prior to that time it was much higher. I feel certain that in the next five years our figures will be much better. One reason for this high mortality is that 4 of the 7 deaths have been from operations on recurrent tumors and the universal experience has been that the mortality on recurrent eighth nerve tumors is vastly higher than when the initial operation has been a radical one.

There are certain points in the operation and postoperative treatment of these tumors which, if overlooked, spell disaster. These tumors lie, as a rule, in contact with the vagus and glossopharyngeal nerves and are usually imbedded in the side of the pons. Sparing these nerves is all important. The dissection must be carried out slowly and with meticulous attention to hemostasis. This is one of the few cranial operations in which electrosurgery cannot be used freely. The heat from the electro-

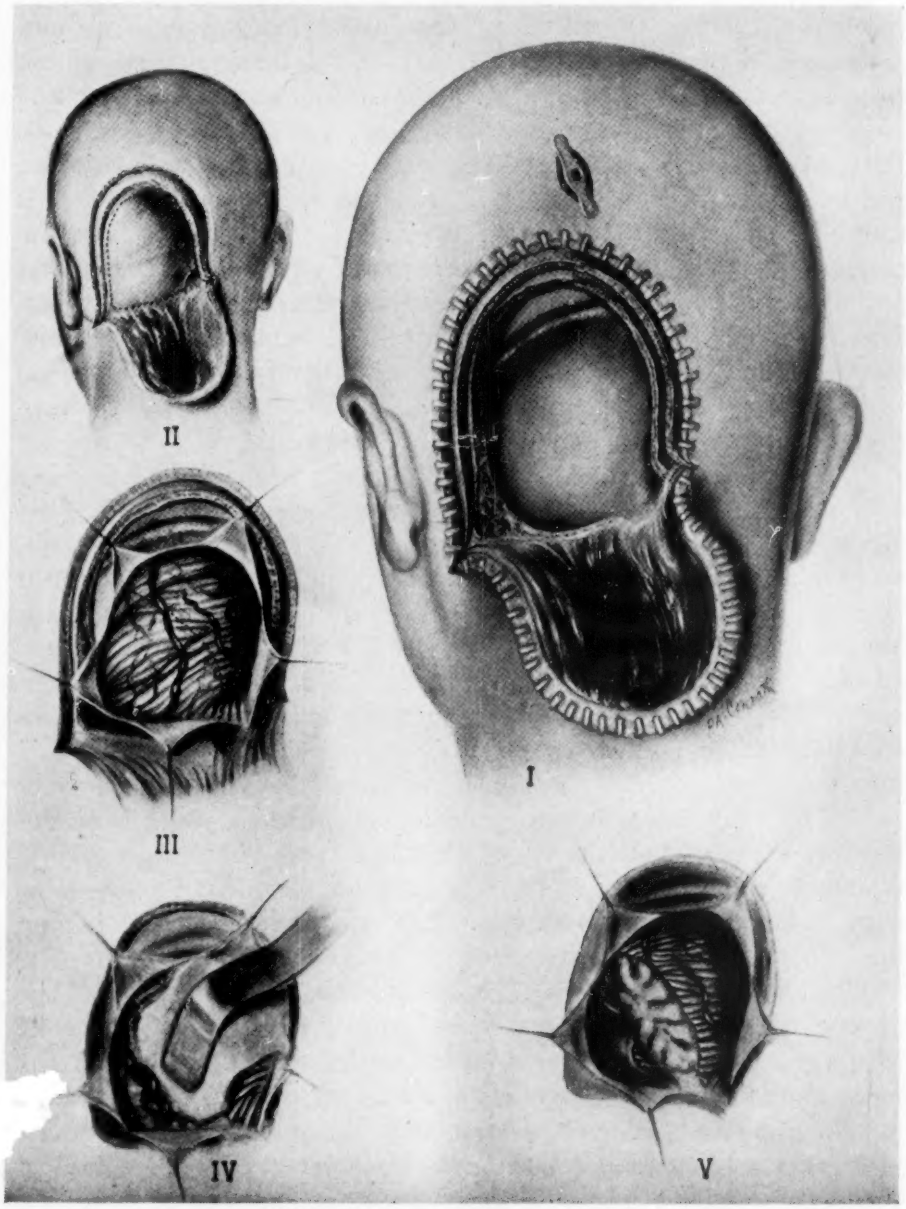

Fig. 5.—Steps of unilateral exposure of acoustic neuroma. (From Sachs: Surgery of the Acoustic Nerve, Nelson's Loose Leaf Surgery of the Ear, Charles C Thomas, Publisher.)

surgical unit may injure the pons or the vagus nerve. Such injury may interfere temporarily or permanently with the patient's swallowing or speaking. This must be kept in mind in the postoperative care. I have lost several patients, in years gone by, because I have permitted these patients to be given food or water too soon; as a result they developed pneumonia. The routine today is absolutely nothing by mouth for a day or two and then only feeding through a small nasal tube until we are certain the patient swallows normally.

Medulloblastomas, Oligodendrogliomas, and Ependymomas.—We now must consider the tumors that are less favorable; many of these are not encapsulated and show some tendency to malignancy. They fall into three groups: medulloblastomas, oligodendrogliomas, and ependymomas. The first of these, medulloblastomas, occur most frequently in children, and usually in the posterior fossa. It is the one brain tumor that is markedly radiosensitive. This fact has given rise to a rather lively controversy regarding its treatment. One group of surgeons believes that medulloblastomas should be treated with deep therapy and not be operated upon at all. A second group believes in doing merely a biopsy and then giving therapy, while a third group believes in doing a radical excision and following it up with x-ray. I cannot discuss today the various arguments held by the proponents of these different theories but shall say merely this, that I personally do not believe in treating any case with x-ray unless the histology of the tumor is known. Radical removal followed by deep therapy, if the tumor is the radiosensitive type, seems to me to hold out the best chance for the patient. Up to the present time, treatment of deep-seated lesions by x-ray or radium therapy only, has not in our experience accomplished either what radical removal has accomplished or, still better, radical removal plus therapy. Using therapy without knowing the pathology of a tumor has the further serious objection that a mistake in diagnosis may readily occur and that a tumor, which is not at all radiosensitive yet perfectly operable, may be treated by x-ray instead of being removed by operation. Such treatment involves a loss of precious time. It is impossible either from clinical symptoms or from x-ray findings to know whether or not a tumor belongs to the radiosensitive variety. One can do no more than suspect this. Furthermore, employing the therapeutic test is hazardous, for there may be a temporary recession of symptoms which gives one a false sense of security. This past year we have had exactly this experience. A child with a posterior fossa lesion had been treated with x-ray. For a few weeks there was some improvement so that x-ray treatment was repeated in spite of a steady advance of symptoms. When the child was brought to us, its condition was such that we had to operate promptly, and we found and removed a cholesteatoma. This rare type of tumor—we have had only eight in our entire series—is not affected by x-ray therapy at all, but is quite readily removed.

The two other types which I am considering in this group, oligodendrogliomas and ependymomas, are not radiosensitive. They grow slowly but are more likely to recur after operation because they are not encapsulated and their margins, therefore, not so well demarcated. These tumors can sometimes be completely removed. It is always an advantage to the surgeon if he knows, or may suspect before he undertakes an

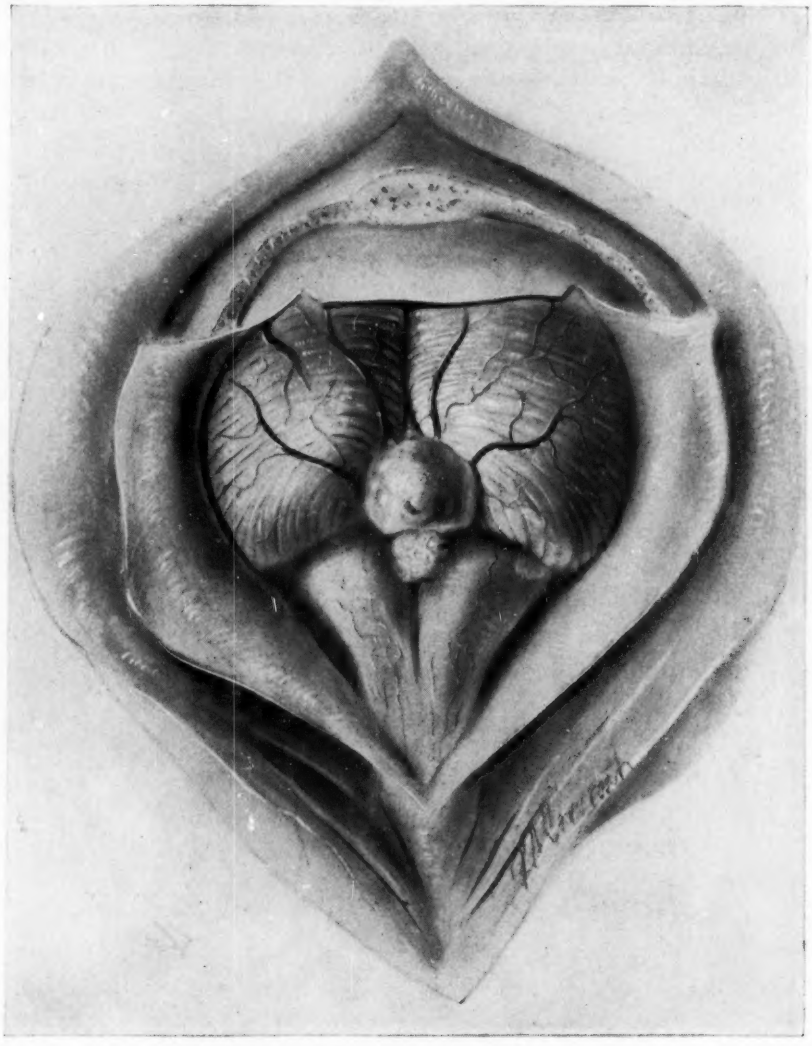

Fig. 6.—Papilloma of the fourth ventricle.

operation, the nature of the tumor. This is frequently possible with these tumors because of the peculiar type of shadow they cast in the x-ray plate (Fig. 1). Given this clue, the cautious surgeon plans his operation somewhat differently, for these tumors frequently extend well beyond the areas of calcification; consequently one must provide ample room for their removal by making larger bone flaps.

There are a good many other tumors which I have grouped under the heading miscellaneous. No one type amounted to more than 1 per cent. The prognosis for some of these is very favorable, such as papillomas of the choroid plexus, which usually are located in the fourth ventricle (Figs. 6 and 7), or cholesteatomas. Others in this group are malignant and have a poor prognosis. None of them warrants special discussion here since they do not present any different diagnostic or surgical problems.

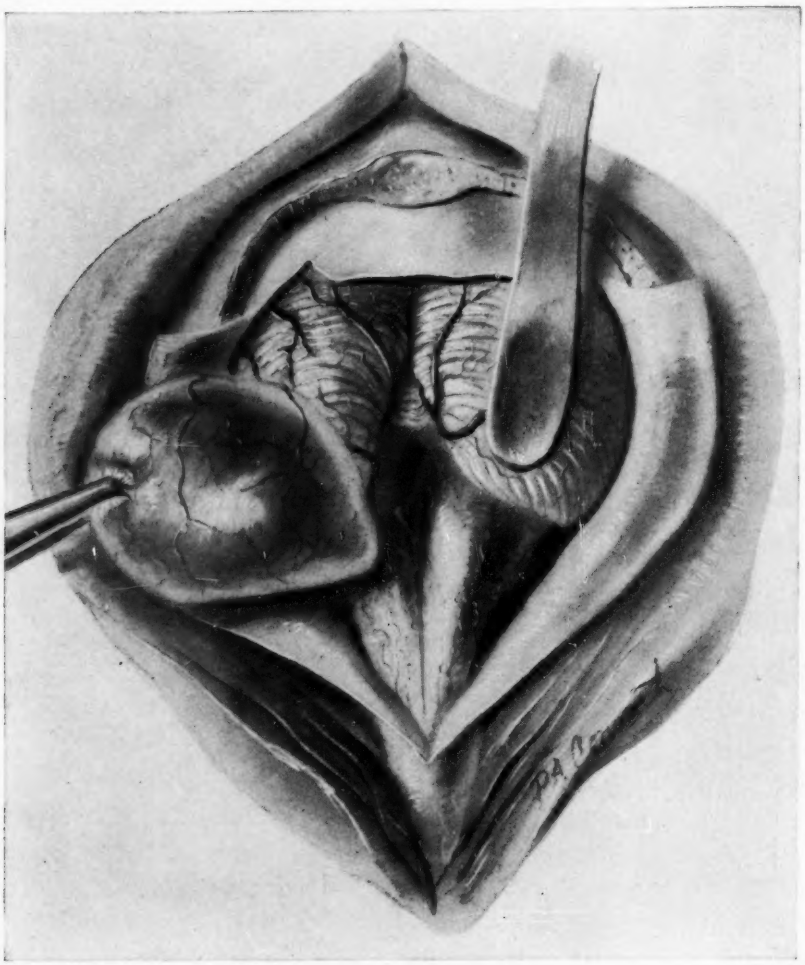

Fig. 7.—Papilloma of the fourth ventricle.

Pituitary Tumors.—The pituitary tumors, however, present problems which are entirely different from those of any other intracranial tumors. Practically the only symptom that brings patients suffering from a pituitary lesion to operation is loss of vision. This loss of vision is different from that caused by a brain tumor; it is characterized by a peculiar field defect, bitemporal blindness, and by the absence of choked disc.

This visual disturbance is produced in a different way; it is due to direct pressure on the optic chiasm. Because of the peculiar arrangement of the fibers in the chiasm, when the pressure is exerted equally on the two sides, typical bitemporal blindness occurs. In the rare cases in which the pressure is not symmetrically exerted, the field defect may be of a different type.

The operative treatment has been well standardized. Whereas there was a time when cases of pituitary disease with an enlarged sella turcica were operated upon through the nose, transphenoidally, today all neurological surgeons do these operations by an intracranial route. In fact, the only one who still employs the intranasal approach is Hirsch, formerly of Vienna, now in Boston.

The advantages of the intracranial procedure are: (1) a sterile field which, even under the most favorable circumstances, the nose cannot be; and (2) a larger field which permits adequate exposure of the tumor and enables the surgeon to undertake a more radical procedure. The one disadvantage is the risk of hemorrhage into the tumor bed after operation. This, however, requires meticulous hemostasis and very careful postoperative observation so that, if a hemorrhage occurs, the clot may be promptly evacuated. My own custom, in case of doubt, is to drain the sella for twenty-four hours to avoid this complication.

In the course of years I have found that some of these patients have recurrences; this can be obviated best by postoperative deep therapy. I do not believe in treating a pituitary tumor case, in which there is marked loss of vision, with deep therapy first, and operating only as a last resort. The danger of losing vision permanently while trying x-ray therapy—for weeks or months may elapse before one can know whether x-ray helps—is a risk I am unwilling to take.

Spongioblastoma Multiforme.—Lastly, we must consider the malignant type of glioma, the spongioblastoma multiforme. Here is a field in which much still has to be done, for, up to the present time, very few patients with this type of tumor have been permanently cured. These tumors are infiltrating and rapidly growing and, as a rule, patients with this type of tumor die within two years after the onset of symptoms. How best to deal with these cases has given rise to considerable discussion. It is usually impossible to make the pathologic diagnosis before operation. One may suspect this type when the patient's symptoms develop rapidly, but this is uncertain and practically all cases with brain tumor must be operated upon. Many of these can be diagnosed grossly at the operating table. The difference of opinion that arises is how to deal with the case if one finds a malignant glioma. One group of surgeons advocates doing nothing but a biopsy and closing up; a second group advocates taking out as much of the tumor as possible and sewing up the dura tightly; the third group, in addition to removing as much of the tumor as possible, leaves a large decompression to relieve the pa-

tient's pressure symptoms if and when the tumor recurs. Experience has shown that the first method, not to attempt to remove the tumor, gives no relief whatever and is attended by an immediate, very high postoperative mortality. On the other hand, removing the tumor usually gives the patient complete relief from his headache and saves his eyesight, while the focal symptoms, such as paresis and aphasia, may clear up. Then, if the dura has been closed, when the tumor recurs the patient dies quickly. This second group does not believe, ever, in operation a second time upon a patient with this type of tumor.

I belong to the third group. I do a decompression after a radical removal with the idea of giving the patient relief as long as possible. If there is *no* decompression, the patient who gets a recurrence suffers as much as he did before his first operation, while in this way he may be quite comfortable, often to the very end. I do believe, in some cases, in operating repeatedly, two and three times even, if by so doing the patient can be kept comfortable and does not have too much disability. Of course, the family must understand that this is only a palliative procedure and will not effect a cure.

I can see no justification for the attitude of the first group since their procedure not only hastens the end but often precipitates it. I can see the point of view of the second group; however, in my experience, the majority of families want their relatives' lives prolonged if possible, and I for one am not willing to recommend euthanasia. My point of view is excellently expressed in that fascinating book, *As I Remember Him*, recently published by Hans Zinsser, late Professor of Bacteriology at Harvard, when he says: "I have always come to the conclusion that the safest principle, except in a few special instances, such as the last stages of cancer, leukaemia or of Hodgkin's disease, is to continue to work with all means at one's disposal as long as the pulse keeps going and the breathing continues."

In the past ten years our percentage of tumor removals, partial or complete, has greatly increased and, in the past five years, it has amounted to from 95 to 97 per cent of all tumors operated upon, and, though we are more radical than we used to be, our mortality is going down. We are removing tumors now that we didn't venture to tackle ten years ago, notably tumors in the ventricles. This has been made possible by the extensive use of electrosurgery. Any incision into the brain used to be a formidable procedure, but that time has passed. Today we have no hesitation in incising it and even excising large blocks of tissue. A great aid also in these procedures, especially if we are dealing with an infiltrating glioma, is a suction apparatus.

Eight years ago we changed our method of anesthesia and now use practically nothing but avertin with the addition of local anesthesia. We have given avertin in over 2,000 cases and find it more satisfactory and safer than any other anesthetic we have ever used. It requires a

skilled anesthetist to administer it, and there are little tricks upon which its successful use depends. This method of anesthesia has contributed greatly to better results. Not only has avertin been eminently satisfactory, but it has been a great relief to both patient and surgeon. As we use it, the patient knows nothing about his operation and does not even know when he is put to sleep. It is administered in his room, in bed, and the patient is not moved until after he is asleep. Frequently the patient inquires the next day when he is going to be operated upon; whereas, when a patient has been operated upon under local anesthesia, and has required a second operation, he has often dreaded the ordeal and begged for a general anesthetic. Patients who have had avertin do not have this dread.

I have pointed out what a serious problem the malignant gliomas constitute. With the idea of solving this problem, we tried deep therapy directly into the open wound during the course of an operation, but, after trying it for a number of years, we could not convince ourselves that the results were any better than formerly and rarely use it any more.

Though we now know how to relieve patients with infiltrating gliomas, their cure has not yet been solved.

On the diagnostic side we have had no very significant advances, but we have come to make more use than ever of ventriculography. With greatly increased experience our interpretation of air plates has naturally improved. We have found that a large number of views from different angles have helped us to localize difficult lesions more accurately.

We have been trying out electroencephalography and have found that, in a considerable number of cases, it confirms localizations made by other methods. Sometimes it has indicated focal lesions of which there was no evidence by any other diagnostic procedure, and these patients, when operated upon, had no demonstrable lesion. On the other hand, in some cases of meningioma, electroencephalographic examination showed no evidence of a lesion as there is no electrical activity in a tumor itself. For these reasons, therefore, I feel that, though the study of electroencephalographic records is of great interest and may in the next few years yield valuable information, it cannot now replace other recognized methods of diagnosis. In my clinic, at present, we do not feel that we can place great dependence upon it.

Today, just as ten years ago, we rely for our diagnosis primarily on our history, physical examination and ventriculography.

It is just as necessary today as it always has been for men to keep their feet on the ground and learn to evaluate both diagnostic and surgical procedures properly. Anyone—well, almost anyone—can acquire the technical skill to operate, but the most valuable asset for the neurological surgeon always has been and still remains—*judgment.*

THE MECHANICAL SUPERIORITY OF ANNEALED STAINLESS STEEL WIRE SUTURES AND LIGATURES

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THE RELATIVE dependability of surgical suture materials should be part of the fundamental knowledge of every surgeon. If one type of suture material is used routinely for all surgical procedures, the operator may overlook other materials of superior efficiency from lack of familiarity with the various types.

The strength of healing wounds depends upon three main factors: (1) The mechanical resistance of tissues, sutures, and knots to tension; (2) the local tissue reaction caused by suture material, trauma, or infection; and (3) constitutional disease which alters the normal healing process. Dehiscence of abdominal or other wounds is favored by a combination of mechanical factors and biological factors. Mass ligatures, tightly drawn knots, and continuous tight big-bite suturing predispose to local necrosis, infection, and separation of the wound edges. The tension forces in a wound are borne alike by the tissues and by the sutures which hold them together. Strength of sutures and integrity of surgical knots are of obvious importance in maintaining the approximation of wound edges. An important biological factor which favors dehiscence of wounds is the weakening of tissues and delay in healing resulting from the local inflammatory reaction caused by organic suture materials. The sheep protein of catgut produces a marked tissue reaction, the scleroprotein of silk a less pronounced response, and inorganic (wire) sutures the least unfavorable changes.[2]

The favorable clinical results obtained with annealed (18-8) stainless steel wire sutures and ligatures have been in sharp contrast at times with the unfavorable results and failures seen in certain instances where organic sutures (catgut and silk) were used. From laboratory studies and observations on the surgical wards it was found that sutures of stainless steel wire favored the optimum healing of wounds. This prompted the investigation here presented to determine by comparative tests the mechanical efficiency of the several types of suture materials commonly used in surgical practice.

Method of Testing Tensile Strength of Sutures.—The tensile strength was determined by the sudden application of a 20 kg. pull on a 5 cm. length of each suture. The apparatus (Fig. 1) consists of a calibrated cylindrical testing scale suspended from the transverse top piece. Two clamps which hold the suture are hung upon the testing scale. A rectangular platform between the lateral uprights bears a 20 kg. weight which is hoisted and joined to the lower clamp. When this platform is suddenly released, pull is exerted upon the segment of suture in the

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vertically arranged testing scale and clamp system. A ratchet on the testing scale facilitates an accurate reading as it prevents the calibrated scale from snapping back when the suture breaks. In this way a reading is obtained of the maximum force which the suture segment withstood before breaking.

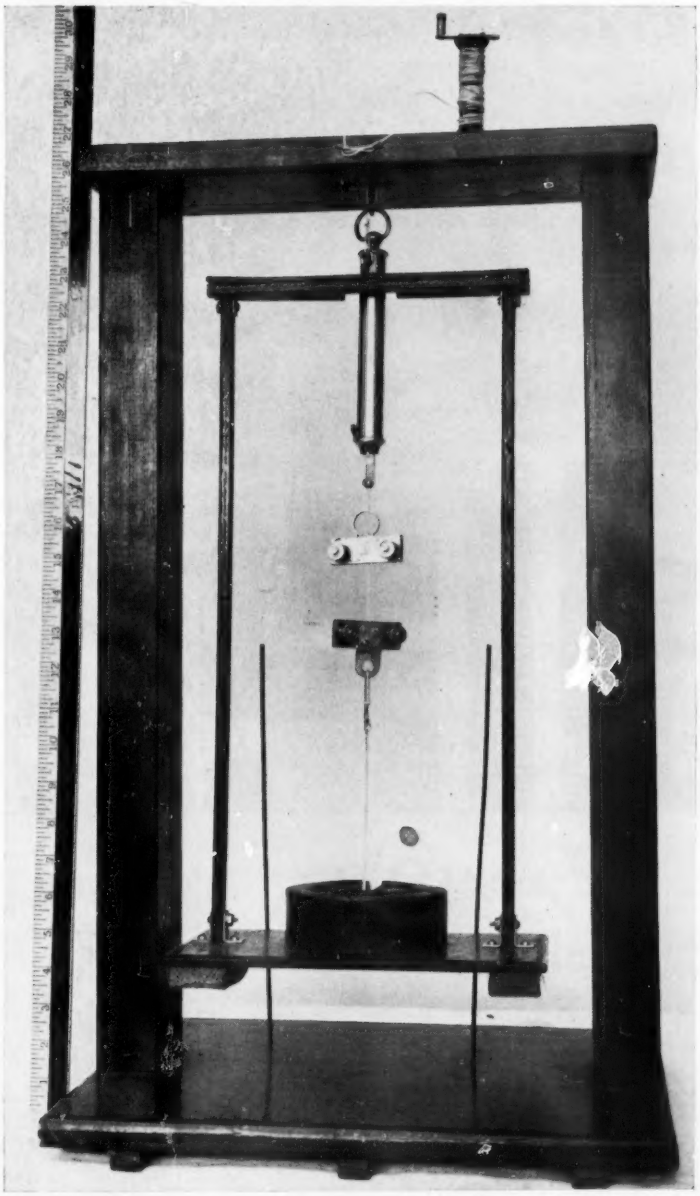

Fig. 1.—Apparatus for testing the tensile strength of sutures and the holding strength of knots.

Tensile Strength of Sutures.—In order to compare the tensile strength of any given suture material with another, it is necessary to determine the tensile strength per unit of diameter for each suture to be tested.

By dividing the tensile strength (grams of pull registered on apparatus) by the diameter of the suture expressed in microns, one can justifiably compare the tensile strength of, say, No. 3 chromic catgut with No. 1 silk by expressing their tensile strengths as grams per micron.

Both large and small sizes of the following materials were used for these tests: plain catgut, chromic catgut, two brands of serum-proof black silk, and annealed 18-8 stainless steel wire. The average of four tests for each size of each material was recorded.

Chromic catgut was appreciably stronger than plain catgut. Silk was only slightly stronger than chromic catgut. Wire was considerably superior in strength to catgut or silk (Fig. 2).

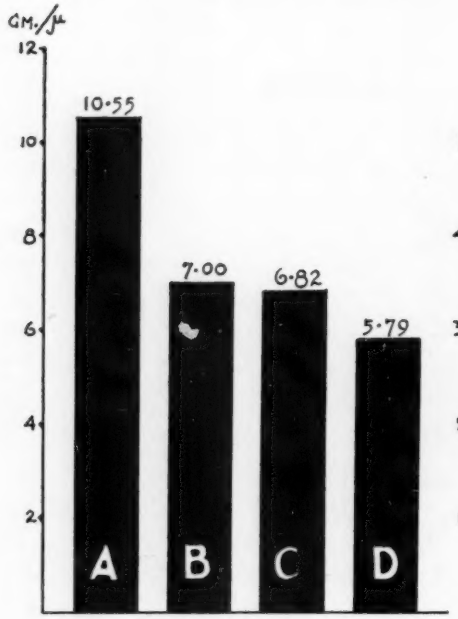

Fig. 2.

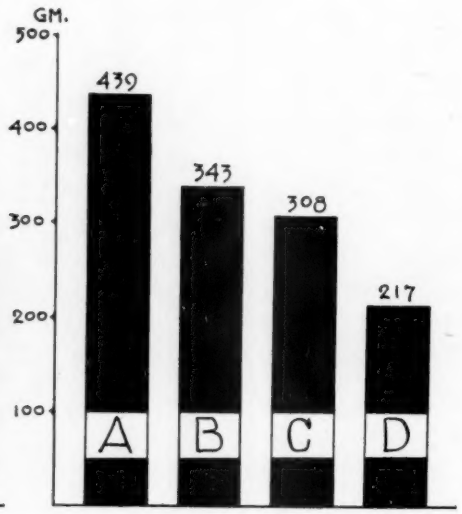

Fig. 3.

Fig. 2.—The average tensile strength of sutures in grams per micron of diameter. *A*, annealed stainless steel wire; *B*, black braided serum-proof silk; *C*, chromic catgut; *D*, plain catgut.

Fig. 3.—The average variability in tensile strength of sutures expressed in grams. *A*, two brands of black braided serum-proof silk; *B*, chromic catgut; *C*, plain catgut; *D*, annealed stainless steel wire.

Variability in Tensile Strength of Sutures.—By analysis of the tensile strength tests it was found that wire gave the most constant values for all sizes. Silk proved to be the least reliable. Fig. 3 is a graphic comparison of the average variability in the tensile strength of silk, chromic and plain catgut, and annealed stainless steel wire. The greater the variability in tensile strength, the less reliable a suture becomes.

Variability in Diameter of Sutures.—Manufacturers do not follow a standard method of grading the size of sutures so that two brands having the same commercial size on the label may vary considerably in the measured diameter of the sutures. Since the diameter is an important determining factor in the tensile strength, the size indicated on the label may be misleading concerning the tensile strength of a suture.

An average of four readings of diameter was made for representative sizes of catgut, silk, and wire. Fig. 4 illustrates these discrepancies in diameter. The greater the variability in diameter of a suture, the less reliable and constant will be its tensile strength. Wire showed the greatest uniformity of diameter.

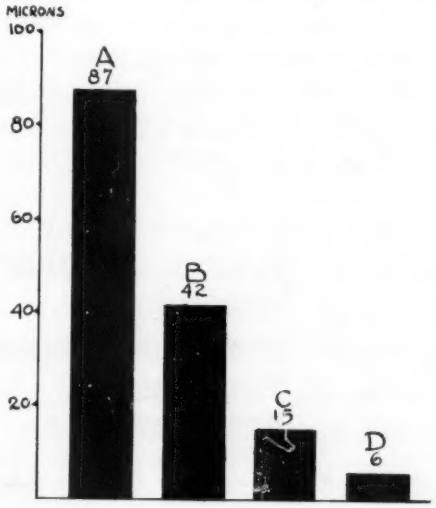

Fig. 4.—The average variability in the diameter of sutures expressed in microns. *A*, chromic catgut; *B*, plain catgut; *C*, black braided serum-proof silk; *D*, annealed stainless steel wire.

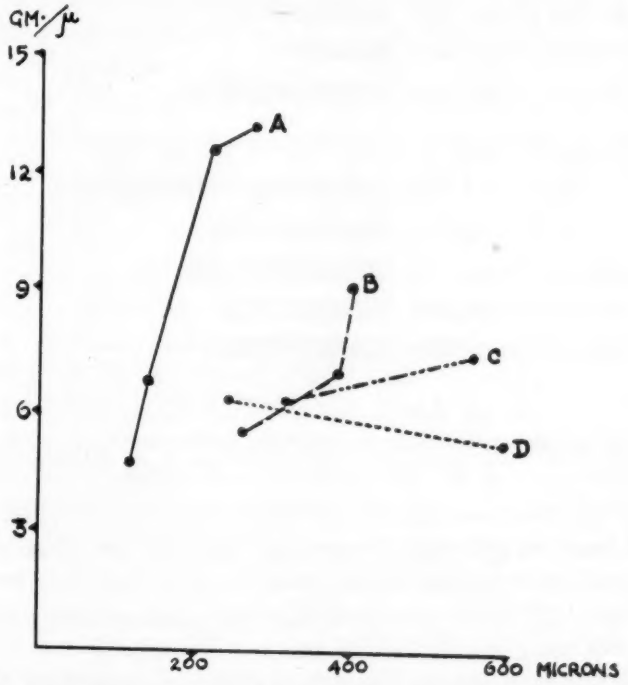

Fig. 5.—The tensile strength of sutures in grams per micron of diameter is plotted against the diameter in microns to show the relative change in tensile strength as the diameter is varied. *A*, annealed stainless steel wire; *B*, black braided serum-proof silk; *C*, chromic catgut; *D*, plain catgut.

Relation of Suture Diameter to Tensile Strength.—In Fig. 5 the tensile strength in grams per micron is plotted against the diameter in microns for various sizes of the four different kinds of suture materials and shows the relative change in tensile strength as effected by varying the diameter. Plain catgut was the only material tested which showed a decrease in tensile strength per unit of diameter as the size of the suture was increased. Stainless steel wire showed a marked increase in tensile strength with relatively little increase in the diameter. The heaviest wire tested was approximately the same diameter as the finest silk and catgut, yet the tensile strength of wire was found to be more than twice that of either silk or catgut.

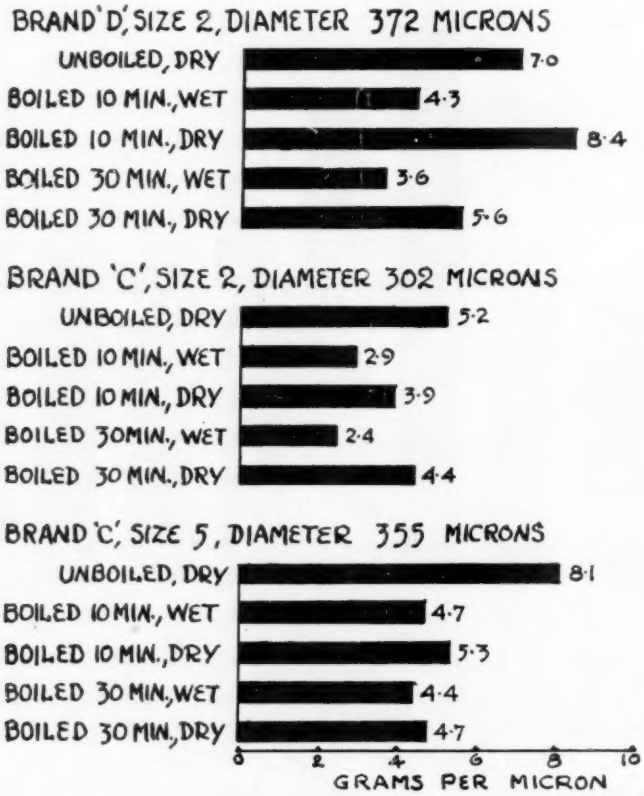

Fig. 6.—The effects of boiling and drying on the tensile strength of braided black serum-proof silk. The tensile strength is expressed in grams per micron of diameter.

Effect of Boiling on Tensile Strength of Silk Sutures.—Wet silk which had been boiled ten minutes was found to have lost one-third of its tensile strength. After being boiled thirty minutes, wet silk had lost about one-half of its tensile strength as compared with dry unboiled silk from the same spool. After the wet boiled silk was subjected to air drying for twenty-four hours, an appreciable part of the original tensile strength was regained.

Fig. 6 tabulates the results of tests on boiled silk sutures.

The surgeon should not expect silk boiled for ten minutes to retain more than two-thirds of its original strength. Further weakening is produced by tying a knot which produces sharp angulations in the suture that will not resist as great a pull as a straight strand.

Method of Testing Surgical Knots.—The following tests were made to determine what kind of suture material and what type of surgical knot were most secure and gave the greatest holding strength. Each suture was tested with a granny knot, a square or reef knot, a surgeon's knot, and a triple-throw knot (tied as two square knots). All knots were tied in a uniform manner by throwing a loop around a circular support and using a hemostat to grasp one end of the suture as an aid in settling each knot down as firmly as possible without breaking the suture. The components of each knot were made to lie in the same plane and traction with the aid of a hemostat was directed in the plane of the loop. This produced flat knots and avoided insecure twisted knots.

The ends of the suture remaining after the knot was tied were cut off with scissors not farther than 1 mm. from the knot. The loop around the circular support was then divided. The 5 cm. segment of suture bearing the knot was made fast in a clamp at each end and tested for holding strength on the apparatus (Fig. 1) which had been used in determining tensile strength of sutures. Sufficient sudden pulling force was applied in all tests to untie the knot or break the suture.

Holding Strength of Surgical Knots.—All plain and chromic catgut knots untied when subjected to the tension test. One-third of the triple-throw knots, made of silk, remained intact, but all of the others (surgeon's, square, and granny knots) untied. All of the stainless steel wire knots, including the granny knots, did not untie in any of the tests.

Catgut and silk knots showed a definite increase in stability of the square and triple-throw knots when the cut ends of the suture were left 5 mm. long. There was no increase in holding strength of granny and surgeon's knots, however, when the cut ends were left 5 mm. long.

Catgut wet with saline solution produced square and triple-throw knots which had twice as much resistance to the pulling force, and, when wet with mineral oil, were five times as resistant. Yet, all these knots untied. Surgeon's and granny knots showed no increase in holding strength when wet with saline solution or mineral oil.

Taylor[3] demonstrated greater friction values for wet catgut as compared with dry catgut. We had expected to overcome some of the frictional forces between the loops of the catgut knots by wetting the suture with mineral oil. The reason why our tests showed an increase in holding strength when this was done is not clear. Oil may make the surface of the suture more porous so that the loops of a knot bite into each other more securely.

Jenkins[1] found that, when the strength of catgut in a wound was dependent upon the knot, the strength lasted only two or three days and failure was due to untying of the knot. The disruption of catgut

knots in wounds is favored by wetting of the suture which causes a swelling with increased elasticity and a tendency for the twisted strands to untwist.

When silk had been wet with mineral oil, the triple-throw knots showed a 70 per cent increase in resistance to the pulling force. The square, surgeon's, and granny knots were essentially unimproved by the oil treatment. Silk could not be wet with saline solution for these tests because of the patented waxy material used by the manufacturers to make the silk serum-proof.

There was no change in the stability of wire knots whether dry, wet with saline solution, or soaked with mineral oil. All wire knots remained tied when tested.

Reduced Tensile Strength in Knotted Sutures.—The percentage of decrease in tensile strength of knotted sutures was obtained by comparing the tensile strength of a straight strand of suture with the tensile strength of a knotted suture in which the knot remained intact and the suture broke when tested. The kind of knot employed had no apparent influence on the tensile strength of knotted sutures.

Plain catgut lost 14 per cent; silk, 24 per cent; chromic catgut, 28 per cent; and 18-8 annealed wire, 30 per cent of their original tensile strength when knotted. Tying a knot in the wire causes stretching which apparently weakens the suture and accounts for the marked reduction in tensile strength of knotted wire sutures.

Disruption of Surgical Knots.—Knots that disrupted when tested were found to untie by a rolling movement of the second loop which carried it over the short cut end. This rolling movement was a rotation of the suture on its long axis. When the second loop had rolled over the short cut end, the first loop slipped and the knot untied. Therefore it was thought that the resistance of a suture to long axis torsion might be a factor in maintaining the integrity of surgical knots.

A special apparatus was constructed to measure the long axis torsion resistance of sutures (Fig. 7). A 1 cm. length of suture under 1 kg. of tension is fixed in the apparatus between two small circular clutches. By adding analytic balance weights to the aluminum weight pan, the jeweled action central axis combined with the suture rotates through an arc indicated by the pointer on a mounted protractor scale. The weight required to rotate the suture through an arc of 90 degrees was determined for each suture. Stainless steel wire, diameter 120 microns, gave the highest reading of 18.07 Gm. The lowest reading was 0.73 Gm. for No. 10 black silk with a diameter of 421 microns. Catgut, when wet, had about one-half the resistance of dry catgut. Wire sutures were fifteen to eighteen times more resistant to the torsion force per unit of diameter than catgut or silk. No evidence could be found to indicate that long axis torsion resistance is of any aid in maintaining an intact surgical knot.

Friction between the loops of a knot is believed to be the chief factor in preventing surgical knots from untying. Stainless steel wire apparently possessed greater friction between elements of the knots than other materials tested for none of the wire knots untied. When a wire knot is tied, the force required to lay each loop down firmly causes the wire to stretch. By microscopic examination, stretched wire was found to have a roughened surface which accounts for the increased friction and greater stability of wire knots.

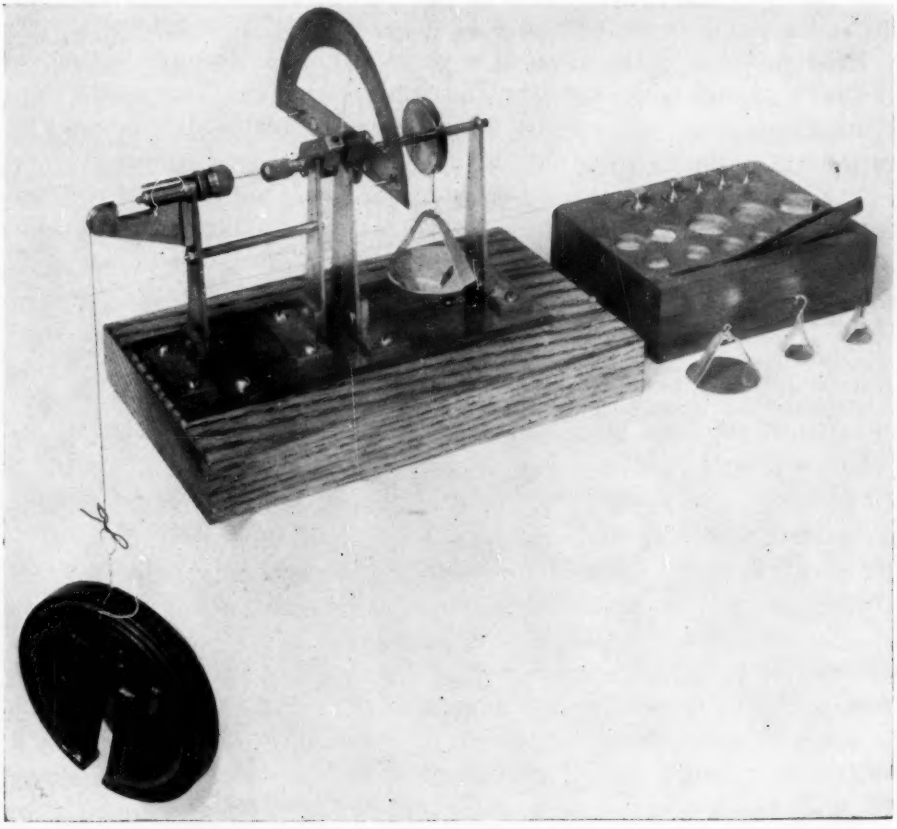

Fig. 7.—Apparatus for determining the long axis torsion resistance of sutures.

SUMMARY

Mechanical tests show that catgut has a lower tensile strength per unit of diameter than silk or annealed stainless steel wire. Catgut knots had the least holding strength when compared with silk or wire. The catgut knot most resistant to a pulling force was the triple-throw knot having free ends 5 mm. or more in length.

The tensile strength of silk sutures is greater than catgut but less than stainless steel wire. Boiled wet silk lost one-third to one-half of its original tensile strength. The triple-throw knot was most resistant to the pulling force for silk. The silk surgeon's knot tended to untie even when the free cut ends were left 5 mm. long.

Annealed stainless steel wire sutures are superior to both catgut and silk in tensile strength and holding strength of knots. The mechanical qualities of wire suture are not effected by sterilization or wetting with saline solution or oil.

The holding strength of surgical knots determined by their resistance to a pulling force places the reliability of these knots in the following order: (1) triple-throw knot (tied as two square knots), (2) square or reef knot, (3) surgeon's knot, and (4) granny knot.

When permeable suture materials are wet with saline solution or mineral oil, there is an increase in the holding strength of their knots.

Friction between the loops of a surgical knot is the greatest single factor in maintaining stability and integrity of the knot under tension. Long axis torsion resistance of a suture plays little or no part in preventing knots from untying.

The superiority of annealed stainless steel wire sutures over silk and catgut as shown by laboratory tests have been confirmed by clinical observations. It is hoped that a wider use in surgery will be found for buried wire sutures.

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THE ROLE OF BRONCHOSCOPY IN THE TREATMENT OF PULMONARY ABSCESS

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THERE is considerable difference of opinion as to the value of bronchoscopy in the diagnosis and treatment of pulmonary abscess. It is not our intention to enter into a discussion of the relative merits of the various procedures which may be employed in the treatment of pulmonary abscess, but rather to present a review of the results that we have obtained over a number of years in the treatment of pulmonary abscess by means of bronchoscopic drainage.

The study to be presented is based on a review of 264 cases of putrid pulmonary abscess seen at the Mayo Clinic over a fourteen-year period, in 193 of which the lesions were treated bronchoscopically. Cases in which the abscess occurred secondarily to tuberculosis, bronchiectasis, and benign or malignant tumor of the bronchus or aspirated foreign body are not included. We have, however, included 6 cases in which there was an antecedent history of a foreign body but in which the foreign body had been aspirated many years preceding the time when the patient came under our observation for pulmonary abscess.

Before attempting to analyze the results that were obtained among the 193 patients treated by bronchoscopic drainage, it would seem advisable to point out briefly the rationale for its use in the treatment of pulmonary abscess. It is of value only in cases in which the abscess communicates with a bronchus. Such a communication is the general rule and is established early during the development of the abscess. When a communication exists, if drainage is adequate, spontaneous resolution of the abscess will generally take place. Lynah and Jackson have pointed out that stenosis of a bronchus communicating with the pulmonary abscess generally occurs, thus interfering with proper drainage and aeration of the abscess cavity. If benefit is to be derived from bronchoscopic aspiration, it is important that the bronchus leading to the abscess be thoroughly dilated. The importance of aeration is especially worthy of emphasis. Brunn, Cutler, and Gross, Allen and Blackman, and others have pointed out that anaerobic organisms are found in approximately 80 per cent of patients with putrid pulmonary abscess, and that undoubtedly much of the benefit that is derived from bronchoscopic drainage is dependent on better aeration of the abscess cavity. In our experience we have been able to establish the most satisfactory dilatation of the stenotic bronchus manually with a heavy pair of dilating forceps. Contrary to Goldman's observation, we have found

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that we can often pass an aspirating tube directly into an abscess cavity, and in many instances we have been able to evacuate as much as 500 c.c. or more of thick necrotic material directly from the abscess cavity itself.

The patients in our study are divided into two groups: the first consisted of 140 patients with pulmonary abscess seen between Jan. 1, 1925, and Dec. 31, 1930, inclusive, of whom 105 were treated bronchoscopically; and the second comprised 124 patients seen between Jan. 1, 1931, and Dec. 31, 1938, inclusive, of whom 88 were treated bronchoscopically. The purpose of the division was (1) to determine whether an abscess that had once been classified as responding satisfactorily to bronchoscopic drainage was likely to recur after a ten-year period, and (2) to determine whether or not we had been able to improve on our bronchoscopic technique so far as results were concerned. Approximately the same percentage of patients in the two groups was subjected to bronchoscopy; namely, 75 per cent in the first group and 71 per cent in the second. The results obtained by bronchoscopic drainage have been approximately the same in the two periods and will be discussed later. It is frequently stated that a pulmonary abscess that has been treated successfully by bronchoscopic drainage will often recur after the treatment has been discontinued. In our experience this has not proved true, because only one patient that we classified as having been treated successfully by bronchoscopic drainage in the period between 1925 and 1930 suffered a recurrence during the following ten years; and in this instance the abscess did not recur at the site of the original lesion but was found in the opposite lung many years later.

SEX INCIDENCE

As might be anticipated, we found that pulmonary abscess occurred much more frequently in men than in women. In our study there were three times as many men as women.

AGE INCIDENCE

No age group is exempt from the ravages of pulmonary abscess. It will be observed in Table I that there was a definite increase in the incidence after the second decade of life and that the maximal numbers of cases in our study occurred during the fifth decade. The youngest patient was 18 months of age, and the oldest 74 years of age. Cutler and Gross expressed the opinion that the prognosis of pulmonary abscess is far better in young adults than in any other age group. This is contrary to our observations, as the best results that we obtained occurred in the fifth decade.

ETIOLOGY

No attempt will be made to discuss the mechanism by which pulmonary abscess occurs. Such an attempt would be especially futile inasmuch as the majority of the patients in our study were not ob-

TABLE I

AGE DISTRIBUTION OF PULMONARY ABSCESS IN 193 PATIENTS TREATED BRONCHOSCOPICALLY

AGE IN YEARS	NO. OF PATIENTS
0–10	7
11–20	10
21–30	36
31–40	44
41–50	58
51–60	26
61–70	10
71–80	2
Total	193

served until some time following the development of the abscess. A review of the etiologic factors concerned in the development of pulmonary abscess is summarized in Table II. It is interesting that the cases which followed surgical procedures approximately equaled in number those which did not follow operation. Tonsillectomy was the most frequent etiologic factor in our series of cases. In approximately 90 per cent of the cases in which pulmonary abscess followed tonsillectomy, the operation had been carried out under general anesthesia. This is not surprising for, as Myerson has pointed out, aspirated material can be demonstrated almost invariably in the tracheobronchial tree following tonsillectomy. Kernan expressed the opinion that the post-tonsillectomy abscess responds more satisfactorily to bronchoscopic drainage than any other type. In our experience, however, no marked correlation was noted between the etiologic factor and the response of the abscess to bronchoscopic drainage.

TABLE II

ORIGINATING CAUSE OF PULMONARY ABSCESS IN 264 CASES REVIEWED

FOLLOWING OPERATION		NOT FOLLOWING OPERATION	
PROCEDURE	NO. OF CASES	ETIOLOGIC FACTOR	NO. OF CASES
Tonsillectomy	60	Pneumonia	52
Dental extraction	33	Acute upper respiratory infection	29
General surgical procedures	31	Trauma	3
Post partum	4	Foreign body	6
		Aspiration of secretion	5
		Unknown	41
Total	128 (48%)		136 (52%)

The location of a pulmonary abscess is of the utmost importance in determining whether or not bronchoscopy is advisable. It is obviously unwise and unjust to attempt bronchoscopic drainage if the abscess is located in such a position that it cannot be reached bronchoscopically. Bronchoscopy would be clearly indicated if it were used for no other purpose than diagnosis, for Kramer and Glass have demonstrated that the bronchial distribution to the lobar divisions is constant in approxi-

mately 85 per cent of cases. If one can determine from which bronchus the purulent secretion is exuding, one can localize the abscess in relation to the chest wall in a highly accurate manner. We were able to establish the exact location of the pulmonary abscess in 229 of the 264 cases included in our study, and the classification as to location in the 229 cases is indicated in Table III.

TABLE III

LOCATION OF ABSCESS AS DETERMINED IN 229 CASES

LOCATION	NO. OF CASES
Right lung, upper lobe	49
Right lung, middle lobe	21
Right lung, lower lobe	64
Left lung, upper lobe	22
Left lung, lower lobe	42
Multiple	31
Total	229

The right lung was the most frequently involved, the lower lobe being the site most frequently selected. Our experience was similar to that of Lukens, that the poorest results as far as bronchoscopic treatment is concerned were obtained in cases in which the abscess involved the lower lobe of the left lung. Contrary to expectation the best results were obtained in those cases in which the abscess involved either the middle lobe of the right lung or the upper lobe of the left lung. A most interesting observation was that slightly better results were obtained in the bronchoscopic treatment of multiple pulmonary abscesses than in that of single pulmonary abscess.

RESULTS OF BRONCHOSCOPIC TREATMENT

In order to evaluate properly the benefit to be derived from bronchoscopic treatment of pulmonary abscess, it is necessary to observe the patients over a sufficiently long period of time. One may often obtain a very striking benefit after a single bronchoscopic aspiration and be misled into believing that the patient is well on the way to recovery. Such may be the case for a short period of time, but a recurrence may frequently take place at this stage. Franklin has shown that, in spite of the fact that a pulmonary abscess appears clinically and roentgenoscopically to have cleared up, an abscess cavity can still be demonstrated following instillation of iodized oil. The factor of recurrence has been taken into consideration in the classification as to results obtained from bronchoscopic treatment in our study. The percentage of recurrence is undoubtedly low. As illustrated in the group of 105 cases in which the lesions were treated bronchoscopically before 1931, in only 1 case classified as improved was there a recurrence of the abscess.

The term cured has been reserved for those patients who have no residual pulmonary symptoms, and for those in whom the roentgenographic changes present in the chest, except for a small area of residual

thickened pleura, have returned to normal. The patients classified as improved may have a mild residual pulmonary symptom, such as occasional cough or occasional expectoration, or there may be incomplete disappearance of the roentgenographic findings (Figs. 1, 2 and 3).

The results that we obtained in 193 cases in which the patients were treated bronchoscopically are listed in Table IV. These figures indeed present an encouraging outlook. They are not unusual, as is readily apparent from a review of the literature, but are in close agreement with the results that have been reported previously by Moersch, Clerf, Tucker, Kernan, and other observers. Indeed, they compare most favorably with the results obtained by surgical treatment as reported by Allen and Blackman, Cutler and Gross, Muller, Lambert and Miller, Moore and others.

A review of the results obtained in treatment of pulmonary abscess during the period between Jan. 1, 1925 and Dec. 31, 1930, inclusive, during which 105 patients suffering from putrid pulmonary abscess were treated bronchoscopically, revealed that satisfactory results were obtained in 65.5 per cent of the cases and that the mortality rate was 5.7 per cent. Sixty-one and one-half per cent of the 88 patients treated bronchoscopically during the period between Jan. 1, 1931, and Dec. 31, 1938, inclusive, obtained satisfactory results, and the mortality rate was 3.3 per cent. In other words, very little improvement has taken place during the past decade in our ability to cope with this lesion bronchoscopically.

TABLE IV

RESULTS OBTAINED FROM BRONCHOSCOPIC TREATMENT IN 193 CASES

RESULTS	NO. OF CASES	
Satisfactory		
Cured	83	64%
Improved	40	
Unimproved	53	31%
Questionable	8	
Dead	9	5%
Total	193	

In 5 of the 9 cases in which patients died, as indicated in Table IV, empyema was associated with the abscess, and probably an attempt to treat these patients bronchoscopically should not have been made. In the remaining 4 cases, pneumothorax and pulmonary edema caused the deaths of the patients.

We found that the duration of the pulmonary abscess before treatment was instituted was the most deciding factor in the prognosis. This apparently applies both to surgical and to bronchoscopic management of pulmonary abscess. The duration of the abscesses at the time the patients came under observation is listed in Table V. The shortest period was one week and the longest was ten years. That the duration of the abscess is an important factor in prognosis is well exemplified by

Fig. 1.—Pulmonary abscess of two months' duration following tonsillectomy under general anesthesia. *a*, Before; *b*, after bronchoscopic aspiration.

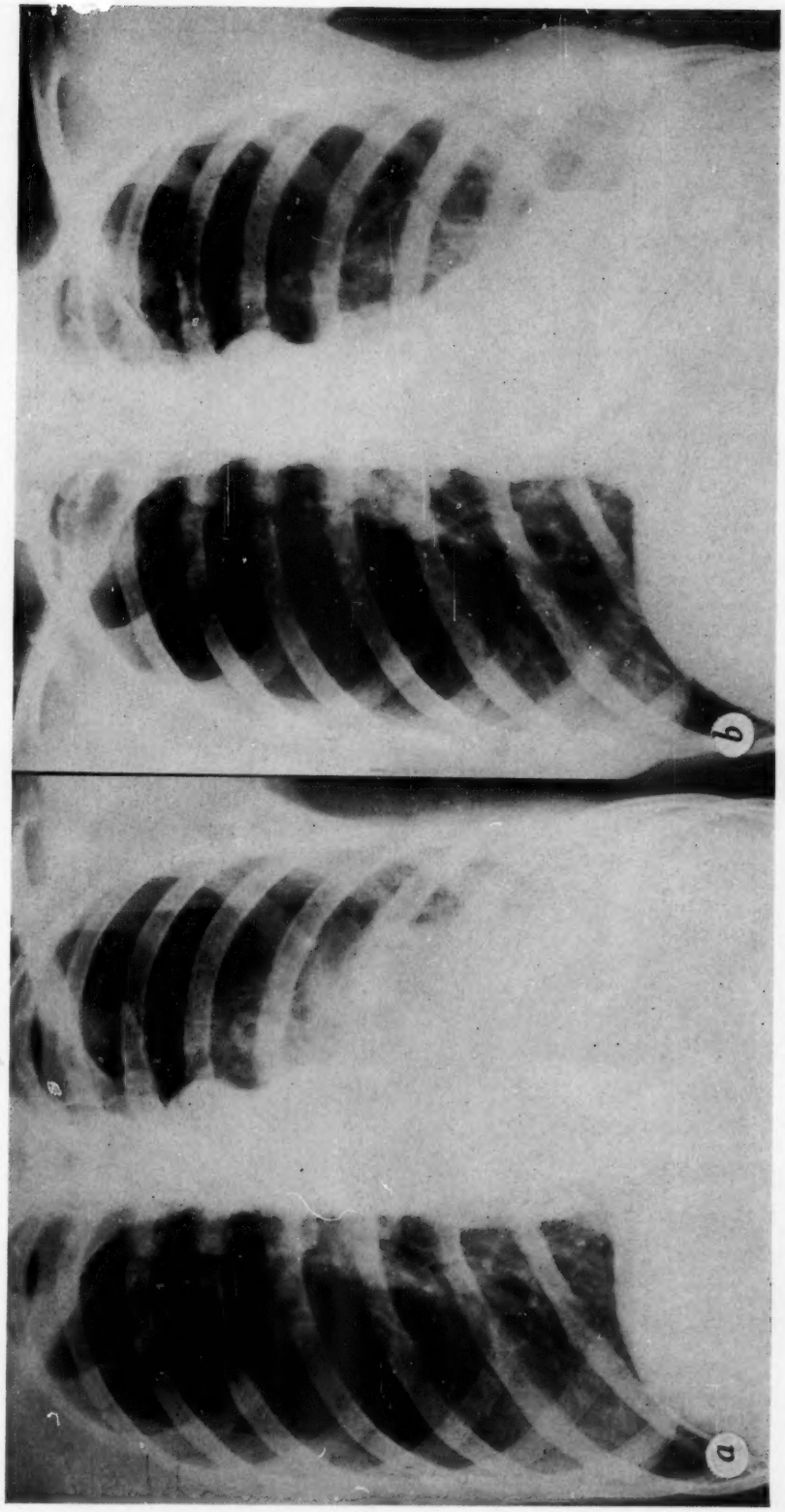

Fig. 2.—Pulmonary abscess of six months' duration, postpneumonic. *a*, Before; *b*, after bronchoscopic drainage.

Fig. 3.—Pulmonary abscess of five months' duration, postpneumonic. *a*, Before; *b*, after bronchoscopic drainage.

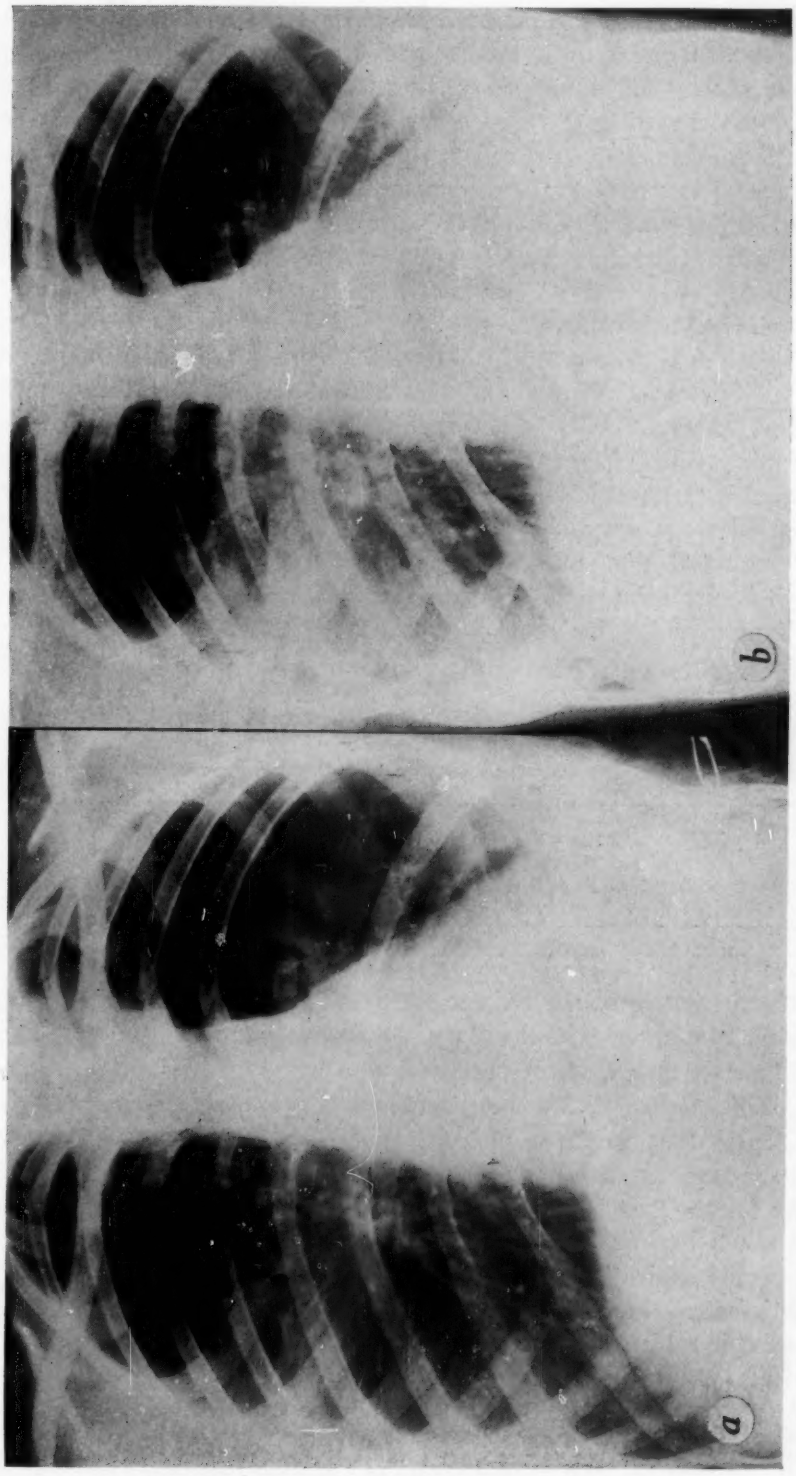

Fig. 4.—*a*, One month following lobectomy an abscess developed in the opposite lung; *b*, the abscess cleared up under medical management.

the fact that in the 19 cases in which the pulmonary abscess had been present less than four weeks, 17, or 89 per cent, of the patients responded satisfactorily to bronchoscopic drainage. In those cases in which the abscess had been present for four weeks but less than three months, the proportion of satisfactory results dropped to 69 per cent, and a still further drop occurred in the percentage of successful results in each group in which the abscess was of longer duration.

Rives, Major, and Romano have very aptly pointed out that most patients with pulmonary abscess are permitted to go an unduly long time before proper medical or surgical intervention is undertaken.

The question naturally presents itself: Just when should bronchoscopic or surgical treatment of pulmonary abscess be instituted? A recent publication of Neuhof and Touroff would seem to indicate that, if surgical intervention is to be carried out, it should be done within the first six weeks. The same rule would seem to hold true so far as bronchoscopic treatment is concerned. Obviously, it is true that in many cases putrid pulmonary abscess will clear up spontaneously (Fig. 4). Lord has stated that but 10 per cent of cases will follow such a course; it is our opinion that this estimate is much too low. Cutler and Gross, Brunn, and Allen and Blackman have reported a much higher

TABLE V

DURATION OF ABSCESS IN 193 CASES IN WHICH THE ABSCESS WAS TREATED BRONCHOSCOPICALLY

DURATION OF ABSCESS	NO. OF CASES
Less than 4 wk.	19
4 wk. but less than 3 mo.	49
3 mo. but less than 6 mo.	50
6 mo. but less than 1 yr.	38
1 yr. or more	37
Total	193

percentage of improvement on medical management. In a small group comprising 26 cases of putrid pulmonary abscess which we treated medically, 13, or 50 per cent, of the cases so treated cleared up spontaneously.* This represents 5 per cent of the 264 cases reviewed.

The course that we have pursued in the past in acute pulmonary abscess has been to keep the patient absolutely at rest and on postural drainage for the first two weeks. If at the end of that time the abscess has not started to resolve spontaneously, we have then proceeded with bronchoscopic aspiration. If the region cannot be adequately drained, or if satisfactory improvement does not take place after two or three bronchoscopic aspirations, we then feel that surgical intervention should be advised. As a rule, if prompt results are not obtained, we do not approve of repeated and indiscriminate bronchoscopic aspirations but

*In these 26 cases the abscess developed while the patient was under treatment at the Clinic. On the other hand, in most of the 264 cases reviewed, by the time that the patient came to the Clinic the abscess had passed the stage at which medical treatment was advisable. It would therefore be incorrect to relate the 13 cases in which the abscess cleared up spontaneously under medical treatment to the total 264 cases.

advocate prompt surgical intervention. We have found that if a successful result is to be obtained by bronchoscopic treatment, three to four bronchoscopic aspirations, as a rule, will suffice. In the entire series of 193 cases which we have treated by this means, 10 was the greatest number of bronchoscopic aspirations carried out in any one case.

CONCLUSIONS

1. Bronchoscopy is of value in the treatment of putrid pulmonary abscess in selected cases.

2. The earlier in the course of development of the pulmonary abscess that bronchoscopy can be carried out, the better the prognosis.

3. Tonsillectomy under general anesthesia has been found to be the most common cause for putrid pulmonary abscess.

4. No correlation has been noted between the cause of pulmonary abscess and its prognosis.

5. If prompt results are not obtained through bronchoscopic drainage, surgical intervention is indicated.

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PRIMARY SARCOMA OF THE STOMACH*

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WE HAVE been stimulated to investigate the subject of sarcoma of the stomach through observing two cases during the last seven years among 135 malignant gastric tumors.

The purpose of this paper is to report these two cases and to review 104 case reports found in the literature of the last ten years, with particular reference to pathology, treatment, and results.

Case 1.—P. L., male, aged 48 years, was seen Dec. 7, 1932, because of an attack of severe abdominal pain which had begun twenty-four hours before and which was followed by abdominal distention, nausea, vomiting, chills, and fever. At irregular times during the past fifteen years he had had attacks of severe pain, just to the left of the umbilicus, which lasted no longer than a few hours and were relieved by bowel movements. No vomiting accompanied these attacks. Intervals of two years occurred between them. About four weeks before admission pain again appeared to the left of the umbilicus and had continued more or less ever since. It was sharp for short intervals only. It was not aggravated by food taking and was relieved by bowel movements. A mild constipation had been present. No blood had been observed in the stools. During the last few weeks he had worked a little in spite of his continued abdominal discomfort. For three days before admission the abdominal pain had become colicky and more severe. It was in the lower abdomen. Two days before a laxative was taken. A bowel movement occurred with some relief temporarily. Soon, however, the pain recurred in more severe form and was accompanied by nausea and vomiting, which were soon followed by abdominal distention and chills and fever. His condition became acute and he entered the hospital. He appeared to be quite sick. His temperature was 100° F. and his pulse was 120. The entire abdomen was tensely distended, tympanitic, and extremely tender. No rebound tenderness was elicited. No definite mass could be felt. No sounds were heard upon auscultation. Hemoglobin was 55 per cent; erythrocytes, 4,000,000; leucocytes, 15,800; differential count, normal. A plain roentgenogram of the abdomen was normal. The patient was observed for twenty-four hours and then the abdomen was explored through a right rectus incision without a definite preoperative diagnosis. Intestinal obstruction was suspected but not found. A very large immobile, nodular mass was felt in the upper abdomen to which the transverse colon was intimately attached. The intestines were greatly distended. The condition was evidently hopeless and the abdomen was closed. Death occurred on the fifth postoperative day.

Autopsy.—In addition to an unaccounted for generalized peritonitis there was found a tumor mass of the stomach. It was both intra- and extraluminal. The intraluminal polypoid portion projected from the posterior wall near the lesser curvature and measured 10 cm. long, 4.5 cm. wide, and 4 cm. thick. It extended from near the cardiac orifice to within 4 cm. of the pylorus. Its mucosal covering was normal except for a craterlike ulcer 2.5 cm. in diameter and 2.5 cm. deep near the cardia. The extragastric portion extended posteriorly and downward be-

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hind the stomach and transverse mesocolon as far as the brim of the pelvis, to the left as far as the hilus of the spleen, and to the right almost to the pylorus. The left half of the transverse colon was firmly attached to its anterior wall. On surfaces made by cutting, the tumor consisted of edematous soft gray tissue mottled with recent and old hemorrhages. The liver was studded with metastatic nodules varying from 2 mm. to 2 cm. in diameter. Such deposits were found also in the retroperitoneal and biliary lymph nodes. Microscopic examination showed dense infiltration of the submucosa and muscularis of the stomach by masses of

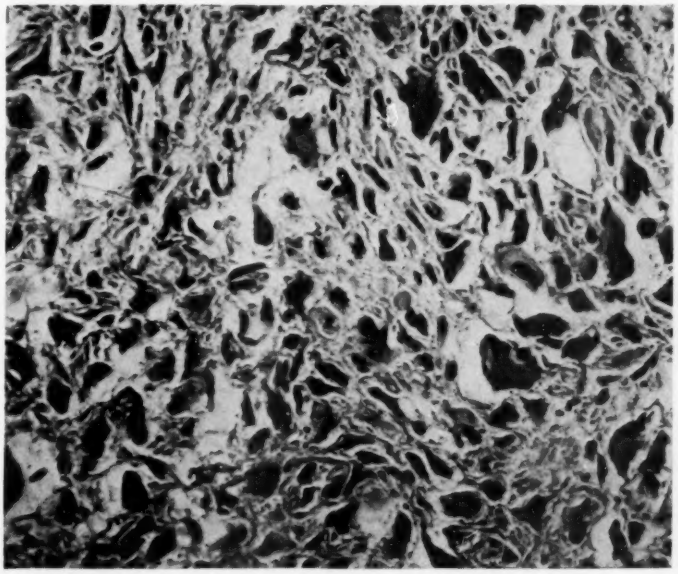

Fig. 1.—Case 1. High power photomicrograph of spindle-cell sarcoma of the stomach. Masses of round and spindle cells are supported by an abundant fibrous stroma. Occasional giant cells with two nuclei occur.

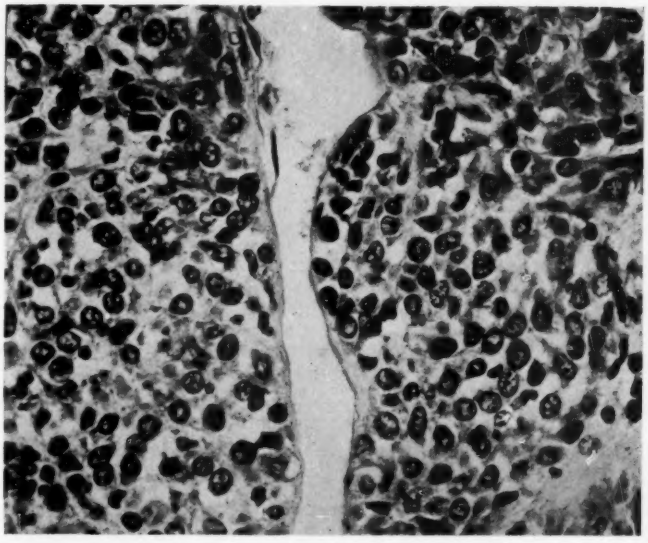

Fig. 2.—Case 1. High power photomicrograph of a metastatic deposit in the liver. The tumor cells are closely packed in a scant fibrous stroma. Most of them are polygonal but many are spindle-shaped. Occasional mitotic figures occur.

round and spindle-shaped cells supported by an abundant fibrous stroma. There were also occasional giant cells with two nuclei. The tumor cells possessed an abundant hyaline pink cytoplasm and round or oval, deeply staining nuclei. The tumor cells of the liver deposits were closely packed in a scant fibrous stroma. Most of them were polygonal with abundant cytoplasm but many were spindle-shaped. Occasional mitotic figures were seen. A diagnosis of spindle cell sarcoma was made.

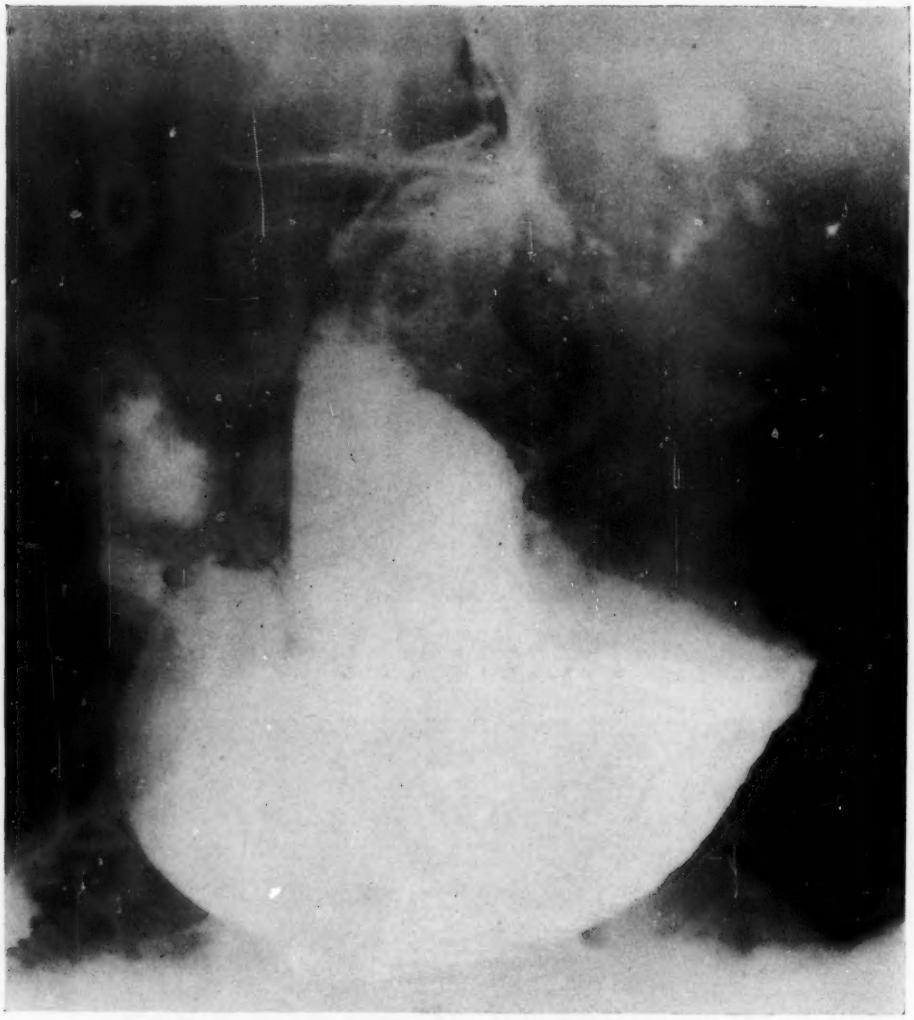

Fig. 3.—Case 2. Roentgenogram showing a large filling defect in the upper portion of the greater curvature of the stomach. This evidence was not sufficient for positively determining the site of origin of the tumor.

CASE 2.—G. G., male, aged 62 years, was seen July 27, 1938. He had felt well until the last five weeks when, at first, his appetite failed and weakness developed. Soon a moderate weight loss of eight to ten pounds occurred. He continued to work for three weeks. Ten days before admission pain was first complained of. It appeared after he had retired as a quite severe colic just to the left of the umbilicus. It continued during the whole night. A physician was called. There was no special examination and no treatment was instituted. Ten days later, which

was the day he entered the hospital, he had a second attack of abdominal pain which was similar to the first. The family physician this time felt a tumor. At no time had there been nausea, vomiting, or any noticeable disturbance of the stools. The only noteworthy physical findings were evident weight loss and a large, firm, nodular mass in the left hypochondrium. It moved with respiration and was not tender. Hemoglobin was 80 per cent; erythrocytes, 4,540,000; leucocytes, 13,700; differential count, normal. One stool examination showed no occult blood. Roentgenologic examination after a barium meal showed a large filling defect in the upper portion of the greater curvature of the stomach. Some of the barium spread out over the region of the palpable mass and here the rugae were seen to be widely spaced.

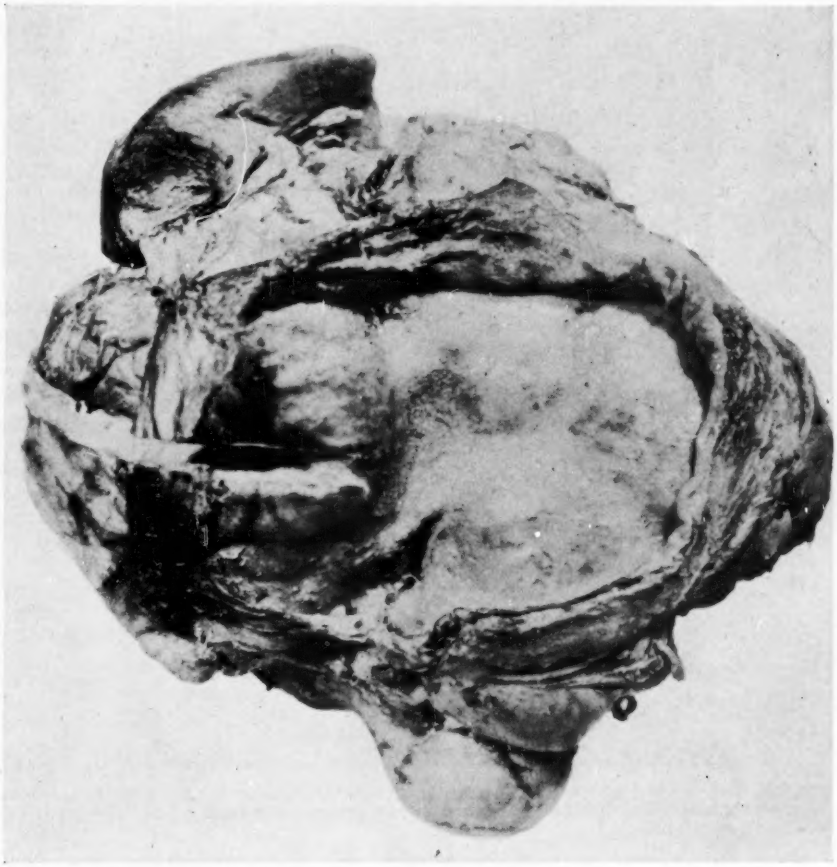

Fig. 4.—Case 2. Photograph of the resected gastric segment involved by the sarcoma together with the attached spleen.

Movement of the mass shifted the stomach and indicated an attachment between the two. Normal peristaltic waves were seen in the lower third of the stomach. There was no gastric residue at the end of six hours. This roentgenologic evidence was not sufficient for determining positively the site of origin of the tumor; it was thought, however, to arise in the stomach. A preoperative diagnosis was made of a tumor probably primary in the stomach but of undetermined type. Through an upper left rectus incision on Aug. 5, 1938, an enormous nodular tumor mass was exposed. All of the surrounding viscera were firmly and extensively adherent to it; particularly was this true of the spleen. The tumor was found to arise from the greater curvature of the stomach and to be resectable. A sleeve type of re-

section, which included the adherent spleen, was performed. An uneventful recovery followed. The patient gained twenty-eight pounds and felt well during the following eight months. At this time roentgenologic examination after a barium meal showed nothing abnormal except a small stomach. Soon afterward he began to fail. He was next examined eight months later, which was sixteen months after he was first seen and operated upon. A tumor was palpated at the site of the first mass and x-ray examination revealed evidence of a recurrence in the stomach. A second operation on Nov. 17, 1939, confirmed these findings. Several metastatic deposits were observed in the liver. The immediate convalescence from the exploratory laparotomy was uneventful. Death occurred two months later.

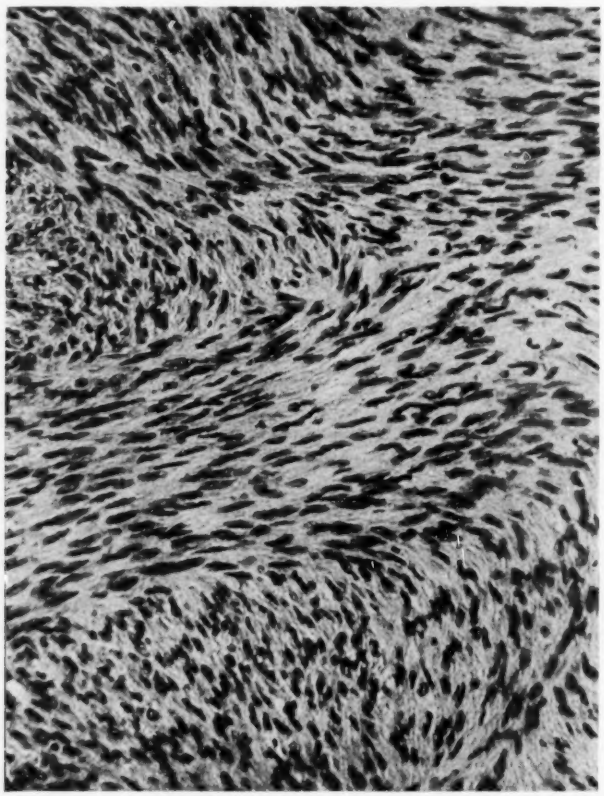

Fig. 5.—Case 2. High power photomicrograph of leiomyosarcoma of the stomach. Masses of spindle-shaped cells are arranged in interlacing bands and whorls. Mitotic figures are abundant.

The mass removed at the first operation, including the spleen, weighed 2150 Gm. It measured 20 cm. long, 16 cm. wide, and 13 cm. thick. The spleen was normal in size. The tumor was found to be of gastric origin. The stomach mucosa over it was intact. The muscularis was completely infiltrated by the growth. A central cyst 10 cm. in diameter was found to contain necrotic tumor tissue. The whole tumor was nodular. Microscopic examination revealed masses of spindle-shaped cells arranged in interlacing bands and whorls. The nuclei were oval, varied considerably in size, and contained a finely granular scattered chromatin. The cytoplasm was abundant. Mitotic figures were abundant. Morphologically the cells suggest those of smooth muscle origin. The tumor was seen to arise in the muscularis of the stomach. Its mucosa covering was very thin but intact. *Diagnosis:* Leiomyosarcoma of the stomach. No evidence of metastases was found at the first operation or upon subsequent examination of the tissue removed.

TABLE I

CASE REPORTS OF PRIMARY SARCOMA OF STOMACH COLLECTED FROM LITERATURE SINCE 1930

AUTHOR	NO. OF CASES	AUTHOR	NO. OF CASES
Askey, Hall, and Davis	1	Hunt	1
Balabon	1	Husted	1
Barzell	1	Iacobovici and Stoia	1
Basso	1	Johnson et al.	1
Baumgartner	1	Jones and Carmody	1
Blasi	1	Jordan	1
Brereton	1	Karpe	1
Brocai	1	Klimko	1
Bukowski	1	Lawson	1
Cabot Case 18262	1	Lefort	1
Cabot Case 19222	1	Matyas	1
Cabot Case 19372	1	Melnick	1
Cabot Case 19401	1	Mendelson	1
Cabot Case 20471	1	Middleton	2
Cabot Case 21112	1	Pack and McNeer	7
Cabot Case 23312	1	Pattison	2
Cabot Case 23512	1	Phillips	2
Cabot Case 24501	1	Phillips and Adam	1
Cardillo	2	Phillips and Kilgore	1
Case	1	Pick	1
Cazzamali	1	Ransohoff and Dickson	2
Cheever	1	Reeves	2
Clar	1	Reutschler and Travis	1
Collins	1	Roffo and Gondolfo	1
Collins and Carmody	2	Romeo	1
Comando	1	Schiff and Foulger	1
Counseller and Collins	1	Schultz	1
D'Aunoy	4	Shioda	1
Drane	1	Singer	1
Edwards and Wright	1	Spitzenberger	1
Fedorow	1	Suck	1
Fiessinger and Bergeret	1	Taylor	5
Forbes	1	Venable	1
Freeman	1	Voeckler	4
Glenn and Douglas	1	Wagner	2
Golob	1	Walters and Church	1
Gosset et al.	1	Yardumian	2
Hameed	1	Zellhoefer	1
Harney	1	Zoph et al.	1
Howard and Speer	1		

According to current opinion 1 to 2 per cent of all primary gastric malignancies are nonepithelial tumors. There are approximately 400 case reports in the literature, of which more than one-fourth have been published during the last ten years.

Nonepithelial tumors of the stomach do not all reveal histologic evidence which is final concerning their malignancy. Malignant forms are occasionally confused with anaplastic carcinomas.

Benign tumors not infrequently and carcinomas only occasionally, therefore, may be erroneously included in this as well as in all other such collections.

Confusing terminologies and classifications reveal the unsettled state of this subject among pathologists. We are not concerned here with these controversial matters, which for the most part are of academic interest

only. We have employed, therefore, a simple classification and have centered our attention chiefly upon the two large tumor groups to which nearly all belong; namely, the spindle-cell sarcomas and the malignant tumors of lymphoid origin.

Twelve tumors, probably all of lymphoid origin, were reported as round-cell sarcomas and because of this have been given a separate classification here, without, however, a description separate from that for the tumors of lymphoid origin.

Six other tumors are likewise grouped together for reasons which will be revealed later.

TABLE II

	SPINDLE-CELL SARCOMAS	MALIGNANT TUMORS OF LYMPHOID ORIGIN	ROUND-CELL SARCOMAS	UNCLASSIFIED	TOTAL NO.
No.	39	47	12	6	104
Sex	Males 22 Females 17	Males 33 Females 14	Males 8 Females 4	Males 4 Females 2	Males 67 Females 37
Average age	48.4	42.5	39.5	42.33	44.3
No. operable	29	31	10	4	74
Percentage operable	74.33	64.7	83.3	66.6	71.7
Gastric resection	19	30	10	3	62
Excision	10	1	0	1	12
Operative fatalities	3	7	1	0	11
Percentage of operative fatalities	15.7	22.5	10	0	14.8
No. explored without removal of tumor	5	11	0	2	18
No. and percentage of exploratory operative fatalities	4 80 %	5 45.5%	0 0 %	1 50 %	10 55.5%
No. and percentage of unoperated cases (all died soon after examination)	5 12.8 %	5 10.6%	2 16.6%	0 0 %	12 11.5%
No. treated by radiation alone, all after exploratory laparotomy	1	4	0	0	5

The spindle-cell sarcomas arise from smooth muscle and connective tissue of the ordinary and perineural variety and include the tumors usually referred to as leiomyosarcoma, fibrosarcoma, and neurogenic fibrosarcoma. Among other names in current use for these same tumors are malignant leiomyoma, myosarcoma, myogenic sarcoma, myoblastic sarcoma, fibroblastic sarcoma, fusocellular sarcoma, fibrosarcoma of neurogenic origin, and malignant Schwannoma. Not infrequently a histologic distinction cannot be made between these varieties of spindle-cell tumors, particularly in instances of rapid growth and incomplete

cell differentiation. Clinically and surgically, however, they are indistinguishable and, therefore, are considered here as one inseparable class in which are found thirty-nine of the 104 collected cases.

Sex incidence is not noteworthy. The average age at the time of hospital admittance was 48.4 years. The youngest patient was 13 years of age and the oldest 70 years old. About three-fourths of the cases were in their fifth, sixth, and seventh decades.

For the most part these spindle-cell sarcomas when seen at operation or autopsy are large or massive bulky growths which protrude outwardly to a very marked degree in about one-half the cases and considerably less often project within the gastric lumen to form respectively the so-called exo- and endogastric masses. The former attain the largest size of any stomach tumors. They are occasionally described as being as large as a fetal or an adult head and very exceptionally may weigh as much as 6,000 Gm. Spindle-cell sarcomas of small size are rarely seen. Pedunculated attachments are not infrequent and usually involve only a few square centimeters of stomach wall even when the tumor itself is of enormous size. Growth is by expansion, encapsulated for the most part, and seldom by infiltration or invasion. In extending beyond the stomach at the curvatures these exogastric tumors very often penetrate between the leaves of the gastrocolic and gastrohepatic omentum.

Any part of the stomach may be the site of origin. The proximal divisions seem to be most frequently involved. The orifices, oftener the cardiac, are occasionally encroached upon but rarely if ever obstructed, due in large part, no doubt, to the absence of an annular arrangement. Multiple growths are rare.

Since these tumors arise from the deeper layers of the gastric wall, involvement of the mucosa and serosa, which is frequent, is always secondary. Sooner or later the mucosa overlying these tumors usually becomes involved by single or multiple ulcers which give rise to the bleeding which complicates over one-half of these usually very vascular tumors. This bleeding is often intermittent over a period of months and years and is usually considerable or massive. The serosal surfaces are frequently extensively adherent to the surrounding viscera and peritoneal surfaces.

Extensive degenerative changes occur in a large percentage of the growths to form hemorrhagic and necrotic single or multiple cysts which sometimes become infected and abscessed. These cystic changes of stomach sarcomas are apparently limited to the spindle-cell variety. Deep sinus tracts may extend from the gastric lumen into the degenerated tumor. Necrosis may be extensive but seldom leads to perforation.

Metastases are noteworthy because of their relative infrequency and apparent predilection for the liver. Only 8, or 20.5 per cent, of these tumors gave rise to secondary deposits which were found in the liver as well as elsewhere in 7 instances. Metastasis to the right lung in 1 case constituted the only instance of an extra-abdominal occurrence.

TABLE III

LOCATION OF METASTASES

	SPINDLE-CELL SARCOMAS (8)	MALIGNANT TUMORS OF LYMPHOID ORIGIN (19)	ROUND-CELL SARCOMAS (3)	UNCLASSIFIED SARCOMAS (2)	TOTAL SARCOMA CASES (32)
Regional lymph nodes	2	15	2	1	20
Liver	7	1	0	0	8
Retroperitoneal lymph nodes	1	3	1	0	5
Mesenteric lymph nodes	0	1	0	1	2
Lung	1	1	0	0	2
Spleen	0	3	0	0	3
Diaphragm	0	2	0	0	2
Pancreas	1	2	0	0	3
Gall bladder	1	0	0	0	1
Appendix	1	0	0	0	1
Peritoneum	1	0	0	0	1
Ureter	0	1	0	0	1
Inguinal lymph nodes	0	1	0	0	1
Peritoneal lymph nodes	0	1	0	0	1
Pelvic lymph nodes	0	1	0	0	1
Supraclavicular lymph nodes	0	1	0	0	1
Epicardium	0	1	0	0	1
Medullary cavity long bones	0	1	0	0	1

While radiation is very effectively applied to sarcomas of the stomach of lymphoid origin, it has found practically no place in the treatment of the spindle-cell type. Surgical extirpation by resection or excision is the only curative procedure practiced and was employed in 29 of these 39 cases, which gives an operability of 74.3 per cent. Three, or approximately 10 per cent, suffered operative fatalities. Fifteen were followed for less than six months, if at all. Only 5 were reported to be living and well for a year or more postoperatively and only 1 of all these 39 cases of spindle-cell sarcoma was reported to be living and well longer than five years. These extremely poor results may be more apparent than real in view of the high percentage of incomplete reports. In spite of this they are noteworthy, particularly because of the actual and relatively high percentage of operability of tumors of low-grade malignancy.

The largest division of sarcomas of the stomach in this as well as in

TABLE IV

CASES WITH KNOWN METASTASES AT OPERATION OR AUTOPSY

	SPINDLE-CELL SARCOMAS (39)	MALIGNANT TUMORS OF LYMPHOID ORIGIN (47)	ROUND-CELL SARCOMAS (12)	UNCLASSIFIED SARCOMAS (6)	TOTAL NO. OF CASES (104)
No.	8	19	3	2	32
Percentage	20.5	40.4	25	33.33	30.7

all other collections are the malignant tumors of lymphoid origin which here number 47, or 45 per cent of the total. About three-fourths of them are diagnosed lymphosarcomas, while the remaining bear such names as malignant lymphoma, malignant lymphoblastoma, malignant lymphocytoma, reticulum cell sarcoma, and lymphogranuloma or Hodgkin's disease. While microscopic differences do exist within this group, it is a question how far one should go in expressing these differences in his terminology. The considerable confusion which exists is due not alone to a multiplicity of names but to a lack of uniformity in meaning of the same name when used by different authors or by the same author at different times. Whatever may be the final decision as to whether or not all the tumors in this group represent the same underlying disease process and whether or not the histologic differences noted are of more than academic interest, we believe that the evidence now available justifies for our purpose considering them as an undivided group. Males predominate better than two to one. The average age was 42.5 years. The youngest patient was 3 years and 8 months old and the oldest was 72 years old. Few such tumors occur in the first and eighth decades, but they are found fairly well distributed throughout the intervening decades with a preponderance in this collection in the third and sixth.

They are for the most part single, flattened, diffuse, infiltrative masses which arise from the deeper layers of any part of the stomach, most frequently, however, on the lesser curvature and in the distal third which contained a part or all of the tumor in two-thirds of this collection. Saddle formations at the curvatures with extension to both walls is the rule and single wall involvement the exception. Twenty to twenty-five per cent of the tumors are annular and as such occur in most instances at the pylorus, producing, along with other stenosing types wherever located, an occasional obstruction, which is seldom high grade.

The large size which these tumors occasionally attain is usually due to a more or less uniform or nodular thickening of a large part of the stomach, and less often to a massive projection from a more or less limited area. Exogastric and endogastric lymphoid sarcomas are therefore infrequent and very rarely, if ever, pedunculated. Infrequently leather bottle types and small sharply circumscribed tumors occur.

The overlying mucosa is commonly invaded by tumor cells. Ulceration occurs in over one-half the cases and is frequently superficial but extensive and only occasionally craterlike and deep. About one-third of the tumors bleed. Hemorrhages are large or massive in about one-half of them, and only a few bleed intermittently.

The serosa is invaded in less than one-third of the cases with adherence usually to adjacent surfaces.

The central degenerative changes so common in the spindle-cell type were not mentioned in a single instance among these 47 sarcomas of

lymphoid origin. There were 4 instances of perforation in 3 individuals; in 1 with recurrent perforation this complication followed soon after x-ray therapy.

Metastases are about twice as frequent as in the spindle-cell type, occurring in 40.4 per cent. With three exceptions they were limited to the abdomen, usually to the regional lymph glands.

Thirty-one, or approximately two-thirds, of the tumors were operable. Twenty-nine were removed by some form of gastric resection and 1 by excision. A first stage fatality prevented removal in one instance. Seven, or 22.5 per cent, of these 31 cases suffered operative fatalities. Eleven were followed for six months or less, if at all. Eight, or 25.8 per cent, were living and well for a year or more postoperatively and one-half this number for five years or longer. Metastases were encountered in only 1 of these 8 survivors; he was living and well three years postoperatively and had had no radiation therapy. Radiation in the form of postoperative x-ray therapy was given to only 1 of these 8 cases; it was given in the absence of any known metastases and with a known survival period of one and one-half years. These facts alone, therefore, do not warrant any conclusions for or against postoperative radiation therapy in the treatment of this kind of malignancy. Malignant tumors of lymphoid origin, however, are known to be, as a rule, sensitive to radiation and positive proof of this is found in 4 of the 11 tumors which were surgically hopeless at operation. Radiation therapy alone resulted in 1 apparent six-year cure and 2 satisfactory survivals of more than one year. A fourth survivor was living but not well for six and one-half years. His is a most interesting case. At operation there was found, in addition to an apparently hopeless reticulum-cell sarcoma of the stomach, a perforation of the same which was closed. Inadequate x-ray therapy is stated to have been given postoperatively and to have been repeated one year later in a series of ten treatments. Soon afterward a second perforation occurred near the site of the first and was successfully treated surgically. One is justified in suspecting that the second perforation may have resulted from a softening of the malignant stomach lesion incident to the radiation which was received, since such complications in hollow viscera under these circumstances have been known to occur. Because of this danger some radiologists prefer to radiate such cases after the removal of the primary growth rather than before.

From these data we learn that 6 of 47 (12.7 per cent) cases with malignant stomach tumors of lymphoid origin survived for five years or longer after the institution of treatment, which consisted of surgical removal alone in four instances and of radiation alone in 2 instances. These results, while not good, are much better than in the spindle-cell variety and support the contention that the greatest percentage of five-year survivals is found among the tumors of lymphoid origin which are judged the most malignant.

TABLE V

RESULTS AFTER SURGICAL REMOVAL OF 74 OF 104 STOMACH SARCOMAS

	SPINDLE-CELL TYPE	LYMPHOID-CELL ORIGIN	ROUND-CELL TYPE	UNCLASSIFIED	TOTAL NO.
Operative fatality	3	7	1	0	11
Survival under 6 mo.	11*	5	3	1	20
Survival 6 mo. to 1 yr.	3	2	2	2	9
Survival 1 to 5 yr.	4	4	1	1	10
Survival 5 to 10 yr.	1	3	0	0	4
Survival 10 to 15 yr.	0	0	1	0	1
Survival 15 to 20 yr.	0	1	0	0	1
Insufficient information	4	5*	0	0	9
Living but not well under 6 mo.	0	1	1	0	2
Died under 1 yr.	1	2†	1	0	4
Died under 2 yr.	1	1†	0	0	2
Died under 3 yr.	1	0	0	0	1
Total No.	29	31	10	4	74

*One had postoperative x-ray therapy.
†Had postoperative x-ray therapy.

Two-thirds of the round-cell sarcoma cases were males and their average age was 39.5 years. Three were in the second and four in the sixth decades.

Ten, or 83.5 per cent, were operable and underwent some kind of gastric resection with 1 operative fatality. Only 2 were reported to be living and well a year or longer after operation, 1 for three and 1 for eleven years, in none of whom metastases were encountered.

The 6 remaining tumors bear the following designation: sarcoma, mixed-cell sarcoma, liposarcoma, angiosarcoma, and mesothelioma. There were 4 males and 2 females. The average age was 42.3 years. The one designated only as sarcoma and the two mixed-cell sarcomas resembled tumors of lymphoid origin; whereas, the other three resembled spindle-cell types. All were operated upon and the 2 with evident metastases were simply explored. Four of the tumors were removed, 3 by resection

TABLE VI

RESULTS IN 5 CASES OF SARCOMA OF STOMACH RECEIVING RADIATION THERAPY ALONE

	SPINDLE-CELL TYPE	LYMPHOID-CELL ORIGIN	ROUND-CELL TYPE	UNCLASSIFIED	TOTAL NO.
Living and well 2 mo.	1	0	0	0	1
Living and well 14 mo.	0	1	0	0	1
Living and well 5 yr.	0	1	0	0	1
Living but not well 6½ yr.	0	1	0	0	1
No information	0	1	0	0	1
Total No.	1	4	0	0	5

and 1 by excision. One was living and well nearly three years and was the only one who survived a year.

SUMMARY

Primary malignant nonepithelial stomach tumors comprise about 1 to 2 per cent of all gastric cancers. Most of them are either spindle-cell sarcomas of connective tissue or smooth muscle origin or tumors which arise from lymphoid tissue. Round-cell sarcomas of smooth muscle and connective tissue origin and angiosarcomas occur less frequently.

The degree of malignancy of the spindle-cell type is low. The operability of both groups is notably high. Radiation therapy is very effective in some of the tumors of lymphoid origin.

In spite of these several factors which are very favorable for cure, the results of treatment in both groups are very disappointing.

Of 104 collected and 2 personally observed cases, there were 6 five-year survivals, 1 among 41 with spindle-cell sarcomas, and 5 among 47 with malignant tumors of lymphoid origin.

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CISTERNAL ENCEPHALOGRAPHY

Utilization of Spontaneous Filling of Ventricles With Air Following Withdrawal of Fluid by Cisternal Puncture

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In 1932 Schaltenbrand[1] called attention to the fact that cerebrospinal fluid withdrawn by cisternal puncture, with the patient in the sitting position, allowed the spontaneous introduction of air into the ventricles. This observation was utilized by Schaltenbrand in the development of a method of encephalography that allowed the use of a small amount of air (30 to 40 c.c.) and was designated by him as the "small" cisternal encephalogram. This procedure has been utilized to a considerable extent in Germany and in Scandinavian countries but has had little use in America. According to Schaltenbrand, this method is indicated in cases of progressive cerebral disease without marked increase of intracranial pressure other than epilepsy, suspected cortical atrophy, and suspected pachymeningitis. The method was described as contraindicated in marked arteriosclerosis and marked increase in intracranial pressure.

The use of this procedure in twenty-two cases over a period of the past year has allowed the employment of this method in a variety of cases and provides the experience on which this paper is based.

METHOD

In the patient without increase in intracranial pressure the cisternal pressure is approximately 0 in the sitting position. The withdrawal of cerebrospinal fluid creates a negative cisternal pressure, causing air to be drawn through the needle into the subarachnoid space until the pressure is again atmospheric. As a result, the only equipment needed is a 10 c.c. syringe to withdraw the cerebrospinal fluid from the cistern.

Medication: Two hours before the encephalogram sodium amytal, 0.2 Gm., is given by mouth. Twenty minutes before morphine sulfate, 0.010 Gm., and scopolamine, 0.0003 Gm., are given hypodermically.

The patient is placed in a sitting position, either in bed or in a special chair, such as is used for lumbar encephalography. A nurse, with a hand on either side of the head, maintains its proper position of slight flexion of the neck. After proper preparation of the puncture site a cisternal puncture is made in the usual manner. Because of the lack of spontaneous flow of cerebrospinal fluid, special care must be exerted during the puncture, the syringe attached to the needle, and attempts made to withdraw fluid. When cerebrospinal fluid is obtained, 10 c.c. is slowly withdrawn and the syringe then disconnected from the needle. By listening closely, air can be heard bubbling through the

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needle as it is being drawn into the cistern. When air no longer can be heard passing through the needle, the syringe is again connected to the needle and 10 c.c. more of cerebrospinal fluid is withdrawn. This procedure is repeated until the desired amount of fluid (usually 30 to 40 c.c.) has been obtained.

Immediately following the removal of the needle from the cistern, appropriate roentgenograms are taken. With the small amount of air used, it is necessary to take films in the horizontal as well as in the vertical position. It is only in the horizontal position that the temporal horns may be visualized.

OBSERVATIONS

In the majority of cases in which this method of encephalography was performed, the procedure was utilized to differentiate brain tumor from an inflammatory or degenerative disease of the cerebrum. In no case was the cerebrospinal fluid pressure over 20 mm. of Hg or 250 mm. of water. While the usual procedure was to withdraw 30 to 40 c.c. of cerebrospinal fluid, it was possible to obtain very informative encephalograms with the withdrawal of as little as 15 c.c. in certain cases of brain tumor.

With the use of this method there was not the degree of distress or shock that is associated with lumbar encephalography. Headache, while present, was not severe, vomiting was rare, and there has been little change in the state of consciousness. A significant lowering of the pulse rate has been infrequent and profuse perspiration with pallor has been rarely encountered.

There has been a failure of the ventricles to fill in one case. This patient had a right frontal cystic astrocytoma which was verified by operation at the Mayo Clinic. At the time of cisternal encephalography only 12 c.c. of cerebrospinal fluid could be obtained, and this with difficulty. The x-ray examination showed air in the posterior fossa over the surface of the cerebellum. It has been Schaltenbrand's experience that in those cases where there was a failure of the ventricles to fill with cisternal encephalography a similar failure resulted when encephalography was repeated by the lumbar method.

The type of case in which cisternal encephalography was employed and the results obtained may be illustrated by the presentation of three case reports.

CASE 1.—B. T., a 47-year-old druggist, had been well until four weeks prior to his admission to St. Joseph Hospital on Nov. 27, 1939. The hospital record stated that four weeks before he had contracted influenza and had failed to show a good recovery, in that he continued to lose weight and strength. Because of the complaints of headaches, difficulty in concentration, and nervousness, he had been advised to consult a psychiatrist. Two weeks before admission there developed urgency and precipitancy of urination. Shortly thereafter, there was a slowly progressing left-sided weakness.

This patient was seen in consultation with Dr. G. W. Dishong, and on examination the cranial nerves showed a slight blurring of the optic disks and a slight

lower left facial weakness. Motor reactions showed a mild left hemiparesis. The e was an increase in the deep reflexes on the left, with ankle clonus and a left Babinski response. There was an uncertainty in the left finger-to-nose test, but no true ataxia. There was a decrease in position sense on the left, with astereognosis.

A lumbar puncture was done and was said to have shown a normal pressure and dynamics. The cell count was 3; globulin, negative; Wassermann, negative; colloidal gold curve, 0000000000.

A small cisternal encephalogram was done on Dec. 13, 1939, at which time 18 c.c. of cerebrospinal fluid were withdrawn. The x-ray report revealed no air in the right ventricle, but the left lateral ventricle and the third ventricle were displaced to the left (Fig. 1). A diagnosis of a deep-seated right parietal tumor was made and operation was advised.

Fig. 1.—Case 1. Visualization of displaced left lateral ventricle, after withdrawal of 18 c.c. of cerebrospinal fluid.

On Dec. 21, 1939, an osteoplastic flap over the right parietal area was made by Dr. L. D. McGuire. The tumor was classed as inoperable, a decompression was done, and the patient was returned to his room. On the following morning, the patient died.

At the post-mortem a tumor was encountered in the extreme posterior end of the parietal bone flap. The tumor was covered by about 2 mm. of cortex, was approximately 4 cm. in diameter, and extended about 4 cm. into the brain substance. The location was in the posterior parietal region and did not extend into the occipital lobe. The entire right cerebral hemisphere was markedly enlarged and edematous. The lateral ventricle was almost obliterated by the marked edema. The pathologic report of the tissue was spongioblastoma multiforme.

Comment.—In this case there was originally the question of whether the neurologic disability was due to a tumor or to a degenerative disease. The withdrawal of only 18 c.c. of fluid allowed the introduction of sufficient air to detect a ventricular shift. No air was seen in the right lateral ventricle, but at autopsy the right ventricle was found to be almost obliterated by a massive edema which involved the whole right hemisphere.

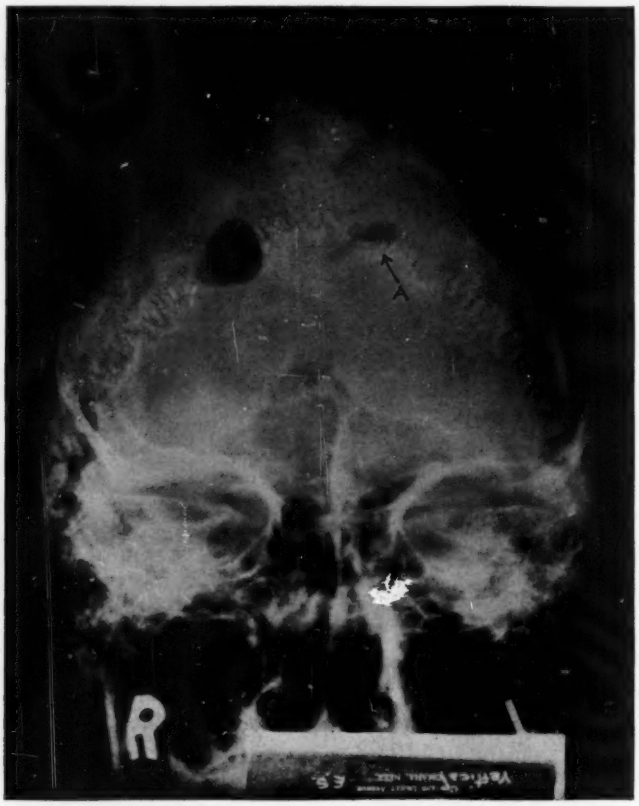

Fig. 2.—Case 2. Visualization of compressed and displaced left lateral ventricle (*A*) after withdrawal of 16 c.c. of cerebrospinal fluid.

CASE 2.—E. R., a 28-year-old farmer, entered the University Hospital Aug. 13, 1939, complaining of headaches for one month, dimness of vision for two weeks, and forgetfulness.

The history indicated he had been well until July 1, 1939, when he began to have headaches, which were chiefly frontal in location. Two weeks before coming to the hospital he had noticed ringing in both ears and seemed to experience difficulty in hearing. At about the same time he began to notice a dimness in vision and difficulty in seeing objects on his right. For the ten days prior to admission he had had severe headaches every day.

Past history, history by systems, and family history were not remarkable.

The neurologic examination revealed upper quadrant right homonymous hemianopsia in the cranial nerves. There was papilledema of 2 diopters on the left and of 1 diopter on the right. There was apparent reduction of hearing on the left. Motor status showed normal motor power, without tremor or disorder in tone. Reflex status showed the deep reflexes to be somewhat exaggerated, but equal on the

two sides. Superficial reflexes were all normal in type. Coordination tests were well performed, although there was some unsteadiness in the right heel-to-knee test. Sensory status showed normal appreciation of all types of sensation.

X-rays of the skull showed the anterior clinoid on the left to be slightly decalcified; the pineal body was shifted 5 mm. to the right and 5 mm. posteriorly.

A cisternal encephalogram was done, with the withdrawal of 16 c.c. of fluid. The cisternal encephalogram showed the ventricles shifted to the right, with apparent compression from the inferior and lateral sides of the left lateral ventricle, which was incompletely filled (Fig. 2). The third ventricle was not visualized. There was no evidence of air in the subarachnoid spaces over the hemispheres.

From the neurologic examination and the cisternal encephalogram, it was felt that there was a tumor in the left central parietal region.

On Sept. 6, 1939, a craniotomy was done by Dr. J. J. Keegan. A large oval pedicle flap was made over the left parietal region. At about 3 cm. depth in the left temporal parietal region a brain tumor was exposed and partially removed. A microscopic section of the tissue removed at the time of operation was diagnosed as astroblastoma.

Comment.—In this case the neurologic findings pointed to a left temporal parietal tumor. This was confirmed by the withdrawal of a small amount of fluid (16 c.c.) from the cistern, which showed a compression of the left lateral ventricle and a shift to the right.

CASE 3.—P. C., a 36-year-old business man, was seen Aug. 3, 1939, because of dimness in vision. Nine years before he first had noticed failing vision in his left eye. At that time he was found to have a beginning optic atrophy in the left eye with a gross defect in the lower visual field. A cisternal puncture showed normal pressure, no cells, a protein at the upper limit of normal, and a negative Wassermann test. It was suggested that he might have an early multiple sclerosis. Subsequently, there was little change in vision until June, 1939, when there was an additional blurring in the right eye.

The history by systems was negative and the general physical examination was likewise negative.

The neurologic examination at this time showed a left optic atrophy and a slight papilledema on the right. Otherwise, the neurologic examination was negative.

A cisternal encephalogram was done, with the withdrawal of 50 c.c. of spinal fluid. X-ray films revealed that the ventricles were slightly enlarged, but normal in contour (Figs. 3 and 4). There was no apparent displacement of the median line structures. There was some filling of the subarachnoid spaces in the frontal area. The patient experienced no distress from this procedure and insisted on making a 150-mile drive to his home the following day.

Comment.—The cisternal encephalogram was of diagnostic value in this case which presented a Foster Kennedy syndrome. The encephalogram made it possible to differentiate between an inflammatory disease and a subfrontal tumor. It is also remarkable that this man experienced little distress and insisted upon driving to his home, 150 miles away, the following afternoon.

COMMENT

Davidoff and Dyke[2] stated that good results in lumbar encephalography may be obtained with 70 c.c. of air. As little as 20 c.c. have

Fig. 3.—Case 3. Visualization of anteroposterior view following withdrawal of 50 c.c. of cerebrospinal fluid.

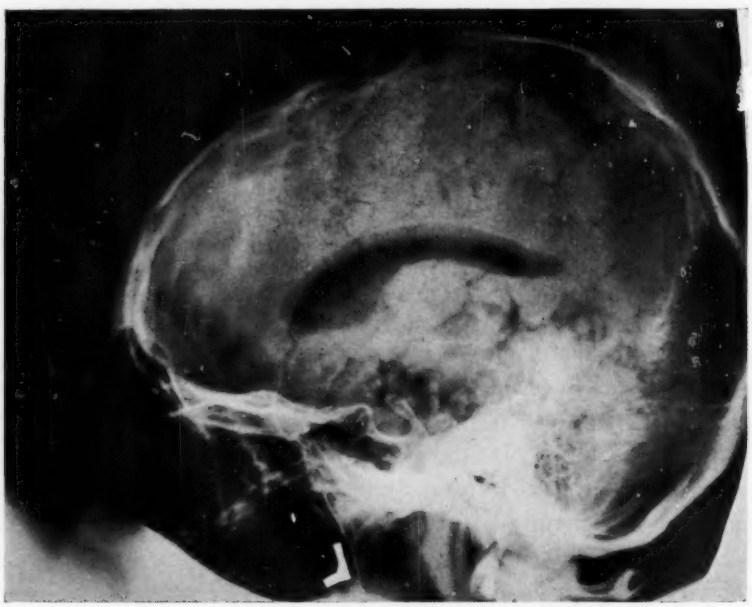

Fig. 4.—Case 3. Lateral view showing visualization of the anterior portion of lateral ventricles. No evidence of distortion suggesting tumor.

been used by Flügel,[3] and Davidoff and Dyke quote Cestan and Riser as using 30 to 40 c.c. Experience with the small cisternal encephalogram of Schaltenbrand would indicate that the withdrawal of 30 to 40 c.c. of spinal fluid allows the introduction of sufficient air to visualize adequately the ventricles, provided films are taken in a horizontal as well as vertical position.

This procedure has a definite appeal because of its simplicity in operation and the relative lack of distress or discomforting sequelae. These features allow a more general use of encephalography.

An attractive feature is that the final cerebrospinal fluid pressure in the cistern is the same in all cases (atmospheric). This provides a certain control that is not present in other methods of encephalography.

It is felt that the cisternal encephalogram reveals valuable information in cases of suspected brain tumor where the intracranial pressure is not remarkably elevated, and frequently the withdrawal of a small amount of cerebrospinal fluid (15 to 20 c.c.) is adequate.

There are definite limitations in the use of this procedure. It would seem that the chief contraindications would be (1) presence of a high degree of intracranial pressure, (2) suspected posterior fossa lesions, (3) signs of a cerebellar herniation with symptoms of neck stiffness and pain. There are perhaps some objections to the use of the cisternal puncture, based upon dangers such as have been described by Dandy.[4] This method would have little use in cases where the chief interest is the cortical pattern, such as epilepsy, because of the tendency of the air to enter the ventricular system before entering the subarachnoid spaces.

CONCLUSIONS

1. The method of cisternal encephalography of Schaltenbrand is described.

2. Experience with this procedure would indicate that it has a place as a diagnostic method where visualization of the ventricular pattern would aid in differentiating types of intracranial pathology.

3. The chief advantages of this type of encephalography are its simplicity, relative freedom from distressing symptoms, and the fact that the final cisternal pressure is the same in all cases.

4. The use of a small amount of air by this method would allow more general employment as a diagnostic aid.

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AN AUTOLOCKING SILVER CLIP

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IT HAS long been common knowledge that metallic silver is well tolerated by the tissues. Silver wire has been successfully employed as a suture material and for many years neurosurgeons have used silver clips for hemostatic purposes. The obvious advantage of using silver clips lies in their simple and effective application, particularly in situations in which the performance of ordinary ligation is difficult or practically impossible; also, their use permits considerable conservation of time and effort. However, these simple compressed folds of silver wire obviously cannot be employed upon large vessels, For this reason it would seem desirable to devise a silver clip which would assure a firm grip upon the tissue included in it and which could not open once it was applied. With this in mind an autolocking silver clip as described below has been devised.

The clip is made from thin ribbons of silver of varying widths and cut in varying lengths, depending upon the necessary size. The silver band is folded to form an angle of approximately 45°. One end is provided with a projecting tip approximately one-half the width of the silver band which is bent so as to point toward the opposite end (Fig. 1). This projecting tip acts as the locking device when the clip is closed. The clips are serrated on their inner surface to assure a firmer grip.

The clip applicator consists of a handle attached to long square rods which have jaws at their ends (Fig. 2). The square rods are so constructed that one slides within the other to produce opening and closing of the jaws. This is accomplished by the lever arrangement of one of the handles with the inner rod. The jaws are especially constructed with grooves into which the clip fits (Figs. 3 and 4). These grooves are approximately as deep as the clip is thick. In the lower jaw near the open end there is a second smaller, deeper, and narrower groove which is crescentic in shape and which serves the purpose of bending the projecting tip of the clip in the locked position when the jaws are closed (Figs. 3 and 4). Another groove is also present in the rod to which the lower jaw is attached (Figs. 3 and 4). This groove is approximately the width of the clip and serves the purpose of receiving the angled part of it so as to assure greater stability of the clip when fitted between the jaws. There is also a thin bandlike spring in this groove which presses against the angled part of the clip (Fig. 4). The purpose of this spring is to keep the clip firmly in place when fitted into the jaws and to expand with the greater length of the clip as it is pressed into the closed position, thus obviating buckling which would otherwise occur (Fig. 4).

The operation of the instrument is extremely simple. The silver clips are easily fitted into the grooves of the open jaws. They spring in readily by being slipped backward from the open end of the jaws. The ves-

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sel or structure to be ligated is placed into the clip and the handles of the applicator compressed. As the jaws are forced into the closed position, the projecting tip of the clip fits into its corresponding groove on the lower jaw, which causes it to be bent around the lower end of the clip, thus automatically locking it (Fig. 4).

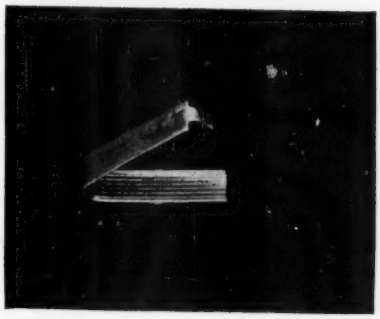

Fig. 1.—Photograph of an autolocking silver clip.

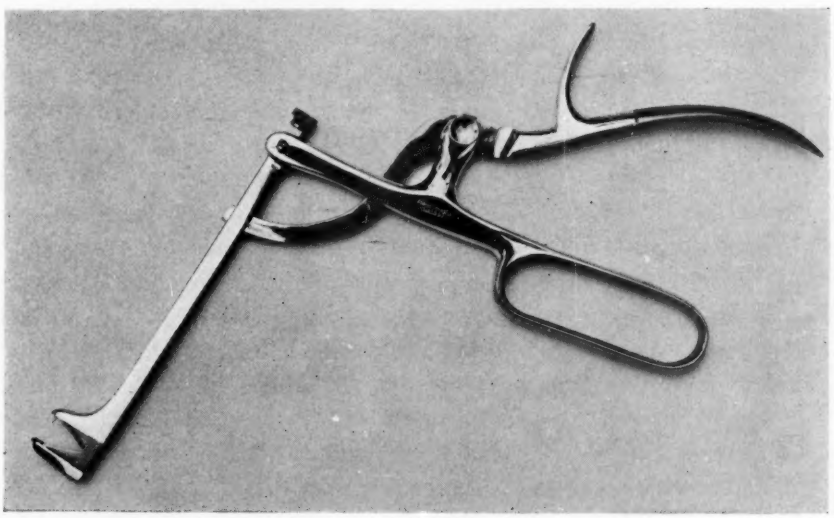

Fig. 2.—Photograph of an applicator containing an autolocking silver clip ready for use.

The clip has been applied experimentally in the performance of various types of operative procedures. Subsequent examination has revealed the clips intact, surrounded by fibrous tissue. Total pneumonectomy has been successfully performed in dogs using only the clips on the hilar vessels as well as on the bronchi and some of the animals are still living, almost a year after the operations were performed. The clip has even been applied to the abdominal aorta in dogs and in no case has it slipped off or failed to produce complete occlusion. No attempt will be made to give a detailed description of these experiments here as they will be presented in a subsequent report.[1]

The clinical application of such a clip is extensive and it is unnecessary to indicate its varied uses. Obviously it is desirable to have available various sizes of clips and corresponding sizes of jaws for their ap-

plication. Since a handle of only one size is necessary, the instrument is so constructed that the jaws can be easily detached from the handle and another size applied. The varying sized clips are made uniformly from lengths of silver ribbon by an especially constructed jig.

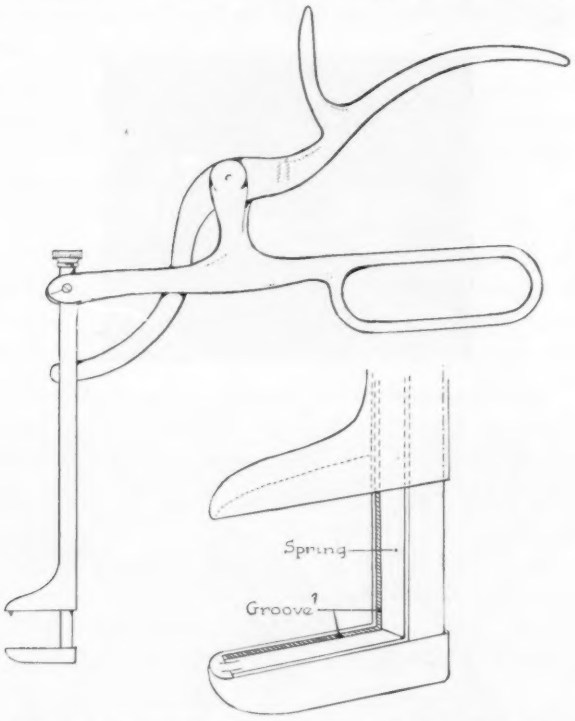

Fig. 3.—Drawing of the instrument showing especially constructed grooves in the jaws.

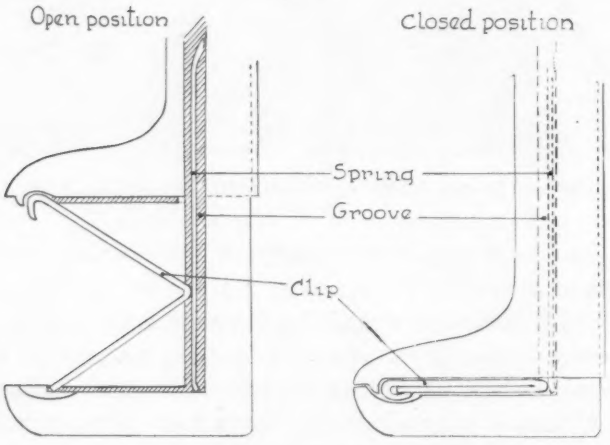

Fig. 4.—Drawing showing longitudinal section through the jaws. In the open position the clip is fitted into the especially constructed jaws. As the jaws are closed and the clip compressed, the projecting tip of the clip is bent around the lower end of the clip, automatically locking it. At the same time the thin bandlike spring is compressed backward to accommodate the greater length of the clip in the closed position.

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Editorial

The Statistical Method

AT THE beginning of the sixth chapter of the *Anatomy of Science*, G. N. Lewis writes: "I am going to speak of the application of a kind of mathematics which, while based on arithmetic, occupies an independent position of great significance. It is a subject which should be taught in every elementary school, but the average educated man has no knowledge of it except that which he may have derived from a practice which society regards as vicious. I refer to the theory of probability, of which the elementary principles are of daily applicability."

While it is true that choice, chance, and probability had their origin in observations relative to gambling, their socially important uses today are in insurance, in dealing with all group phenomena, and in the reduction of scientific observations. Not only are they not taught in elementary schools, they are not taught today in the usual freshman and sophomore courses on mathematics in college, although thirty or forty years ago some account of them was often included in freshman courses on advanced algebra. The daily papers now print so much data from which inferences are drawn that some knowledge of statistics is really necessary to read the papers intelligently enough to avoid misinformation. The like is true of medical and public health professional journals to such an extent that not only the investigator who writes the articles but the practitioner who reads them should have some knowledge of probabilities; indeed, as many of the authors do not have sufficient knowledge of the subject to provide assurances for their inferences, the reader is under the unfortunate necessity of having some such knowledge himself or of having to accept or reject the conclusions quite blindly. One hesitates to urge that a curriculum so crowded as that of the medical schools should make place for a brief course on statistics, but the fact is that this has already taken place in some schools and seems likely to spread to others. Fortunately the elements of statistics are based directly on arithmetic, with only a modicum of school algebra, and are not so very hard to acquire, as Dr. Horace Campbell shows in this issue of the JOURNAL.

—*E. B. Wilson, Ph.D.*
Boston, Mass.

Recent Advances in Surgery

CONDUCTED BY ALFRED BLALOCK, M.D.

HYPERTENSION AND UNILATERAL RENAL DISEASE

REVIEW OF THE LITERATURE AND REPORT OF 16 CASES

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INTRODUCTION

IN THE past few years the fundamental conception of a nephritic and a nonnephritic ("essential") type of hypertension as advanced by Fishberg has undergone some modification, tending toward subdividing this concept into more specific entities. This change may be attributed to (a) many reports of hypertension associated with different types of renal and adrenal diseases and (b) the epochal contribution of Goldblatt on the experimental production of hypertension by constriction of the renal arteries by clamps and the renewed interest in the researches of other investigators.

It is my intention to review briefly some of the important clinical and experimental contributions to the subject of hypertension of the nonnephritic type and to report several cases of hypertension caused by unilateral renal disease which were cured or relieved by surgical treatment. Particular attention and emphasis will be paid to the relation of hypertension to diseases of the genitourinary tract. Individuals interested in the historical background of essential and urologic hypertension are referred to the excellent contributions of Fishberg, Weiss and Parker, Mulholland, Maher and Wosika, McCann, and others.

CLASSIFICATION

A classification of hypertension is extremely difficult due to the complexity of its etiology and pathology and to the rapidly increasing knowledge concerning a variety of clinical diseases which cause hypertension and which were formerly classified under the diagnosis of essential hypertension. Consequently the classical conception of a nephritic and a nonnephritic (essential) hypertension appears to be inadequate. A more comprehensive classification of hypertension has been offered by Schroeder and Steele which is based upon the clinical conditions associated with hypertension and is subdivided into five groups; viz., renal,

nervous, endocrine, vascular, and unclassified. It is highly probable that time and increasing knowledge will prove this classification is also incomplete. It is quite possible that a renal arteriolar lesion which is incapable of being detected by our present diagnostic methods may be the underlying factor in many cases of nonrenal hypertension.

However, it should be emphasized that the exact etiologic relation between many of the disease entities and hypertension is not always clearly or definitely established, for in some instances there is reason to believe that their presence may be coincidental or at least controversial. In fact, some writers even venture to suggest that essential hypertension is not a clinical entity. McCann is of the opinion that in 80 to 85 per cent of the cases of essential hypertension the underlying condition depends upon atheromatous narrowing of the larger renal arteries at or near the aorta and that in 15 to 20 per cent the trouble is due to unsuspected lesions of the kidneys or of the urinary tract.

In the past two years the occurrence of various lesions in the urinary tract of patients suffering with hypertension has assumed greater etiologic significance, as attested by the statistical studies of Schroeder and Steele, Williams and Harrison, and Maher and Wosika and the numerous case reports of Boyd and Lewis, Leadbetter, Nesbit, Bothe, Braasch, Crabtree, and others.

INCIDENCE

It has been only in the past three years that attention has been directed to the occurrence of urologic disease in hypertensive patients. Wosika and Maher recently reviewed 600 cases of hypertension with especial reference to the causative or coincidental factors. They classified 70.97 per cent (425 cases) as essential hypertension or hypertension of unknown type. The remainder, 29.03 per cent (175 cases), were considered cases of secondary hypertension of which 16.5 per cent (99 cases) were examples of urologic hypertension and only 4.34 per cent (26) were cases of parenchymal renal disease; i.e., chronic nephritis, arteriosclerotic kidneys, etc. These authors subsequently published an analysis of the group of urologic hypertensive cases; i.e., 99 cases plus 2 cases of polycystic disease, a total of 101 cases, or 16.8 per cent, of a series of 600 cases. They observed that a single diagnosis seldom covered the entire urologic pathology and that the major urologic lesions were those of obstruction, infection, or a combination of both. The largest group was of the obstruction type, and the approximate levels of obstruction in 72 cases were found to be in the kidney pelvis (5), ureters (18), bladder inlet (9), bladder outlet (38), and unclassified (29). Prostatic disease accounted for 31 cases, or 53 per cent, of the male patients with hypertension. The next largest group contained 27 cases of chronic pyelonephritis and complications in which obvious obstruction was not readily demonstrated. Renal calculi occurred in

17.8 per cent. As a result of this study they concluded that hypertension appears to be associated with urologic pathology more frequently than is ordinarily believed.

Schroeder and Steele studied 218 cases of hypertension and in the renal group of 58 cases, there were 14 cases of glomerulonephritis, 8 calculi, and 4 pyelonephritis. In 29 cases there were factors of stone, infection or obstruction alone, or in combination. In another study the same authors reviewed 71 cases of essential hypertension in young subjects who revealed no renal functional impairment as determined by the ability of the kidneys to concentrate urine and by the standard urea clearance test. Abnormalities of the kidneys and ureters were revealed by intravenous urography in 50 of 71 cases. More than one-half of the patients had some form of urinary obstruction. Harrison and Williams presented a similar study with comparable results. In a series of 100 cases previously diagnosed as essential hypertension, evidence of urinary tract disease was found in 30 patients. In most cases the urologic disease apparently antedated the onset of hypertension; viz., 6 patients gave a previous history of kidney colic, 10 had experienced acute pyelitis, and 3 had unexplained hematuria. Subjective symptoms of vesical irritability and pain in the kidney region were noted in 17 of 30 patients, evidence of urinary obstruction was present in 8 patients, and urinary tract infection was found in 5 patients but was associated with some other factor which may have played a role in causing the hypertension.

Oppenheimer, Klemperer, and Moschkowitz have made noteworthy contributions to the incidence and relation of unilateral renal disease to hypertension. They reviewed 5,000 consecutive autopsies and found the incidence of hypertension in the whole group to be 24 per cent, as compared to 40 per cent in the group of 97 cases with unilateral renal disease. Further analysis of the latter group revealed hypertension to be present in 15 (83 per cent) of 18 cases of unilateral narrowing of the main renal artery, in 21 (32 per cent) of 66 cases of unilateral hydronephrosis and chronic pyelonephritis, and in 3 (23 per cent) of 13 cases of unilateral congenital hypoplasia.

Chute recently reviewed 353 cases of essential hypertension and found 42 cases (12 per cent) with renal lesions; 22 had demonstrable pathology and 20 gave a history of pyelitis or the passage of calculi but did not have complete urinary studies.

Braasch, Walters, and Hammer recently made an important and comprehensive study of the incidence of hypertension in a group of 1,684 patients subjected to renal surgical operation. In this group approximately the same percentage (315 patients, or 18.7 per cent) had preoperative hypertension as that observed in a series of 975 consecutive adult patients taken at random; namely, 195 cases of hypertension, or 20 per cent. In their article a detailed analysis of the

relative incidence of hypertension in association with unilateral renal lesions is presented and frequent reference to their findings is made elsewhere in this paper.

Crabtree and Chaset have recently attempted to evalute the hypertensive tendency in 150 consecutive nephrectomies for severe unilateral renal damage. In this series only 14 cases (9.3 per cent) showed preoperative hypertension; viz., chronic pyelonephritis, 7 cases; hypernephroma, 6 cases; and tuberculous pyelonephritis, 1 case.

EXPERIMENTAL HYPERTENSION

Before undertaking a discussion of the clinical relationship of nonnephritic renal lesions to hypertension, it seems appropriate to review and evaluate the experimental studies on the renal factor in hypertension.

The medical profession is greatly indebted to Goldblatt and his associates for their outstanding contribution in the field of experimental hypertension and for the interest in the clinical aspects of hypertension which their work created and stimulated. Their experiments were performed on dogs and their results have received universal recognition. Utilizing a specially devised clamp, they were successful in producing a persistent hypertension by two methods: (a) partial constriction of both renal arteries and (b) constriction of the renal artery of one kidney followed by the removal of the opposite kidney. A transient hypertension was produced when the renal artery of only one kidney was constricted and the other kidney was left intact. Wilson and Byrom subsequently showed that the latter procedure in rats resulted in a permanent hypertension with all its consequent changes. Goldblatt and his associates demonstrated that the resultant hypertension varied directly with the degree of ischemia induced by constriction of the renal arteries; viz., moderate constriction of the renal arteries resulted in a definite, but not extreme, hypertension which corresponded to that of benign hypertension in man; whereas, severe constriction of the renal arteries led to an early but marked hypertension which was soon followed by renal insufficiency and the picture was comparable to the malignant hypertension in man. Following severe constriction of the renal arteries, small and large hemorrhages and hyalinized and necrotic arterioles were observed in the various organs, except in the constricted kidney which was considered to be "protected" by the renal ischemia.

Following the epochal contribution of Goldblatt there has been a revival of interest and investigation concerning the etiology and renal factor in hypertension. A comprehensive search of the literature has revealed an abundance of experimental studies on this subject which unfortunately has been forgotten or overlooked or whose significance has not been fully appreciated.

Animal experimentation has demonstrated that an increase in arterial tension can be produced by a variety of procedures whose purpose is

to decrease the blood flow through the kidney. This has been accomplished by: (1) removal of large portions of the total kidney substance (Passler and Heineke, Cash, and Chanutin and Ferris); (2) partial ligation of renal arteries (Janeway, Hartwick, Freidman, Collins and Drury); (3) constriction of renal veins (Bell and Pederson and Mendenez); (4) constriction of blood supply by cellophane perinephritis (Page); (5) production of interstitial fibrosis of kidneys by exposure to x-ray (Hartman, Ballinger, and Doub); (6) compression of renal arteries with adjustable clamps (Goldblatt, Lynch, Hanzal, and Summerville and Wilson and Bryom); (7) constriction of blood supply of solitary kidney transplanted to neck (Blalock and Levy); (8) constriction of blood supply of solitary kidney transplanted to groin (Glenn, Child, and Heuer); (9) ligation of one or both ureters (Rautenberg, Hartwick, Harrison, Mason, Resnik, and Rainey, Williams, Wegria, and Harrison, and Blalock and Levy).

Since each of the above procedures causes a decrease in the volume of blood passing through the kidney and is followed by a systemic rise in blood pressure, it has been assumed by many investigators that renal ischemia is the primary or initiating factor in the production of the hypertension. The evidence offered in support of this theory is based chiefly upon deficiency of renal tissue and impairment of renal circulation as accomplished by reducing the total kidney volume by multiple operations (Passler and Heineke), by removing 80 to 85 per cent of the total kidney substance (Cash), or by removing five-sixths of the total kidney substance (Chanutin and Ferris). Further evidence is found in the work of Blalock and Levy, who demonstrated conclusively that the renal blood flow was decreased in dogs with hypertension caused by constricting the renal artery with Goldblatt's clamp.

Drury has described a method for the production of renal insufficiency and atrophy of any grade in rabbits without the production of pathologic changes in the renal epithelium. He employed a loose silk ligature on the left renal artery of baby rabbits to act as a check on renal growth. The diameter of the loop was regulated by tying silk down on wire of known diameter and withdrawing the wire. By this method dwarfed kidneys, varying from 20 per cent to 45 per cent of the total normal combined kidney weight, were obtained and a compensatory hypertrophy occurred in the opposite kidney. He found that a relatively high degree of hypertension develops in renal atrophy before the removal of the compensatory hypertrophied kidney. Following removal of the hypertrophied kidney, the hypertension increased. Secondary changes resulting from renal atrophy included loss of appetite and weight, anemia, disturbance of equilibrium, hemorrhages in the intestinal wall and eyeball, and cardiac hypertrophy.

Recently Jeffers and his associates were able to produce experimental hypertension in nephrectomized parabiotic rats. They found that parabiotic rats survive the removal of both kidneys of one parabiont,

and that following the removal of a third kidney from the other parabiont, the majority of the animals developed hypertension.

However, there is some evidence available to show that renal ischemia is not the only factor concerned in the mechanism of hypertension. Bilateral nephrectomy does not cause an elevation of blood pressure, as shown in experiments of Cash, Hartwick, and Harrison, Mason, Resnik and Rainey. Similar results were obtained following the bilateral ligation of all renal vessels plus bilateral ligation of the ureters by Cash and Blalock and Levy. Goldblatt recently pointed out that the production of hypertension through ischemia appears to depend on the patency of the ureter. He observed that constricting the main renal artery of one kidney causes a systemic rise in blood pressure, but if the ureter of the ischemic kidney is occluded at the same time, no rise in blood pressure occurs. Furthermore the studies of Dock and Rytand on rats with hypertension due to progressive extirpation of renal tissue demonstrated that the blood flow per gram of tissue is as great in such animals as in normal control. Katz, Friedman, Rodbard, and Weinstein found that the severity and persistence of the effect of renal ischemia are dependent upon the ratio of ischemia to normal renal tissue.

The exact mechanism or agents responsible for the elevation of the blood pressure has not been definitely established. Some investigators attribute the increase in arterial tension to a reflex effect from the ischemic kidney; others maintain that this phenomenon is due to the production of a pressor substance in the ischemic kidney. Various experimental evidence has been gathered which tends to refute the "reflex" theory, or, at least, demonstrates that the hypertension associated with an ischemic kidney of the Goldblatt type cannot be prevented or relieved by the following procedures; viz., (1) denervation of the kidney pedicle (Page, Freeman and Page); (2) excision of the splanchnic nerves (Goldblatt and co-workers); (3) complete sympathectomy (Alpert, Alving, and Grimson); and (4) complete destruction of the spinal cord (Glenn, Child, and Page).

The only evidence in favor of a central action of the pressor substance in renal hypertension is found in the work of Dock and Rytand, who showed that the blood pressure of rats with renal hypertension fell to the same level after section of the spinal cord as did the blood pressure of normal rats.

There appears to be ample evidence in support of the formation of a chemical substance in either the ischemic kidney or the unaffected kidney which possesses a pressor effect on the vasoconstrictor nerves or directly upon the blood vessels. As early as 1898 Tigerstedt and Bergman demonstrated the presence of a pressor substance in the saline extracts of normal rabbit kidneys, which they designated as renin. They found that this extract caused an increase in blood pressure when injected intravenously in anesthetized dogs. Fasciolo, Houssay, and Taquini demonstrated the presence of a pressor substance in the blood

of the renal vein of a Goldblatt type of kidney by testing for its vasoconstrictor effects on a toad. However, Boylston, McEwen, and Ivy were unsuccessful in their attempts to demonstrate this substance in the perfusate of ischemic kidneys with Locke's solution. Prinzmetal, Friedman, and Abramson found that saline extracts of ischemic kidneys of dogs and of kidneys of patients dying with benign and malignant hypertension, chronic nephritis, and chronic pyelonephritis yielded greater pressor effects than similar extracts of normal human kidneys. Friedman and Prinzmetal observed that the blood of patients with hypertension exhibited no pressor effect when transfused into patients with normal blood pressure. Katz, Friedman, Rodbard, and Weinstein transferred small amounts of blood from a hypertensive to a normal dog without producing a rise in blood pressure. Solandt, Nassin, and Cowan observed that blood from a dog with a Goldblatt type of kidney produced a transient hypertension in another dog, provided the recipient animal was deprived of both kidneys. Taquini found that acute complete ischemia of the kidney produces a pressor substance as does the partially ischemic (Goldblatt type) kidney.

The physiology and pharmacology of renin have been intensively studied, but the investigators are not in complete accord in their findings. Tigerstedt, Williams, Harrison, and Mason, and Helmer and Page considered renin to be a protein; whereas, Atumi believed it to be a sterol. Tigerstedt, Page, and Merrill, Williams, and Harrison maintained that the pressor effect of renin was elicited by direct action on the blood vessels. The latter investigators have shown that its action is not influenced by elimination of the nervous system, pituitary, adrenals, pancreas, liver, or kidneys. Fasciolo, Houssay, and Taquini showed that the presence of a healthy kidney is capable of diminishing its pressor effects. Tigerstedt and Page observed that successive injections of renin resulted in diminishing pressor responses.

Merrill, Williams, and Harrison studied the effect on the intrinsic circulation of two pressor substances isolated from the kidney; viz., renin, obtained from saline extracts, and a tyrosine-like substance from the autolysate. The former was found to elevate the blood pressure, increase the size of the kidney, increase the blood flow through the kidney, and increase the volume of urine, and its effect was believed to be due to constriction of the efferent arterioles of the glomeruli. These findings were substantiated by Corcoran and Page. The latter substance caused a shrinkage in the volume of the kidney and a diminution of renal blood flow as a result of the constriction of the efferent arterioles. Landis, Montgomery, and Sparkman observed that when the toxic and depressor factions are removed from the crude saline extracts of kidney tissue, the remaining solution elevates the blood pressure without reducing peripheral flow. The Chesleys studied the renal blood flow by means of the diodrast clearance test in 37 women having hyper-

tension and renal impairment occurring separately and together. They found that hypertension sometimes occurs with a normal blood flow and that a marked diminution in renal blood flow may be found in patients with a normal blood pressure. They observed that the urea clearance often parallels the renal blood flow. In the majority of patients having hypertension, the renal blood flow is considerably reduced below average.

Recently Harrison, Grollman, and Williams were successful in extracting from normal kidneys a "renal antipressor substance" which was shown to have no effect upon the blood pressure of normal animals but appeared to possess the property of neutralizing the effects of renin, ephedrine, and other pressor substances. The important significance of these findings is that they offer an explanation of the absence of hypertension in those unilateral renal diseases which one would expect to develop hypertension; viz., the amount of antipressor substance elaborated by the healthy kidney overbalances or offsets the effect of the pressor substance produced by the diseased kidney.

As indicated before, an increase in blood pressure has been produced experimentally by ligation of one or both ureters by Rautenberg and others. Williams, Wegria, and Harrison found that in rats unilateral ligation of the ureter did not always cause hypertension but bilateral ligation always resulted in hypertension, and that the pressor response to renin was more marked in bilateral cases. Blalock and Levy noted that hypertension induced by unilateral ligation of the ureter was abolished by the removal of the affected hydronephrotic kidney. This is in accord with the observation of Goldblatt that the excision of the ischemic kidney, resulting from constriction of one renal artery with a clamp at the height of hypertension, is followed by a prompt return of the blood pressure to a normal level.

Various investigators have reported secondary pathologic phenomena in experimental hypertension which bear a close relationship to the changes observed in clinical cases of hypertension. For example, Gibson and Robinson observed cardiac hypertrophy in dogs with hypertension caused by constriction of the renal artery by a Goldblatt clamp; no constant changes in the blood volume were noted and no impairment in renal function was found. Chanutin and Barksdale observed left ventricular hypertrophy and hypertension in rats following partial nephrectomy. Wilson and Pickering demonstrated acute arteriolar lesions of the malignant variety in rabbits with hypertension resulting from constriction of renal artery with Goldblatt's clamp. They were of the opinion that the incidence of these lesions was related to the degree of hypertension rather than to its duration. Similar changes were found in the arterioles of the intestines, liver, adrenals, eyes, and heart. The arteriolar changes were not found in the ischemic kidney but rather in the contralateral and presumably normal kidney. These changes in the intrinsic circulation of the rabbit differ from those found in human

beings with malignant hypertension. Winternitz and Waters observed gross vascular lesions involving the pulmonary artery, aortic arch and its branches, thoracic aorta, superior and inferior vena cava, and the myocardium, as well as visceral hemorrhages following constriction of the renal artery. The mural changes in the blood vessels were similar to the vascular lesions of malignant nephrosclerosis in man. Wood and Ethridge were able to produce hypertension with arteriolar and glomerular changes in the albino rat by subtotal nephrectomy.

From this mass of interesting, but at times conflicting, experimental data one may safely conclude that a specific type of hypertension may be of renal origin. One of the primary etiologic factors in this type of hypertension is renal ischemia which can be produced in the affected kidney. The exact manner in which this substance exerts its effect on the blood pressure has not been definitely established. Munoz, Braun-Menendez, Fasciolo, and Leloir offered the following explanation of the mechanism of renal hypertension: "Renal ischemia determines the secretion of 'renin.' This protein is an enzyme which acts on a blood globulin ('hypertensin precursor') and gives rise to a substance ('hypertensin') which produces vasoconstriction. Another enzyme, 'hypertensinase,' which destroys 'hypertensin' is present in the blood and tissues." Kohlstaedt and Page recently proposed what appears to be the first definite theory to explain the physiologic mechanism of experimental renal hypertension. They perfused the isolated normal canine kidney with defibrinated blood under varying hemodynamic conditions, and by subsequent pulsate perfusion through the isolated rabbit's ear, studied the pressor effects of venous blood samples which were activated with renin complement ("hypertensin precursor") to form angiotonin ("hypertensin"). They found that the excised normal canine kidney perfused under normal pulsate arterial pressure did not secrete renin into the venous blood, but when the renal artery was partially clamped for 100 or more minutes, the venous blood samples possessed vasoconstrictor properties. From these and other experiments they maintained that the essential factor responsible for the liberation of renin is not changes in blood pressure or perfusion rate but reduced pulsate pressure. On the basis of these experiments they formulated the following theory to explain the mechanism of experimental hypertension: Compression of the renal artery causes a partial conversion of pulsate to continuous blood flow in the kidney with resulting edema and anoxemia of the cells of the tubules. This is followed by an increase in cellular membrane permeability which allows the liberation of the large renin molecule. The liberated renin reacts within renin activator to produce angiotonin which in turn raises the blood pressure and produces constriction of the efferent glomerular arteriole with further tubular anoxemia. Thus a vicious cycle is set up which results in a sustained

arterial hypertension. This interesting and plausible theory requires further clinical and experimental research before it can be accepted.

Grollman, Williams, and Harrison recently reported on the chemical and pharmacologic properties of a renal antipressor substance. They found that when extracts containing the renal antipressor substance were administered orally to normal animals, they did not produce a decline in blood pressure but did have the property of partially inhibiting the pressor effect of subsequently injected renin. When extracts containing a sufficient amount of renal antipressor substances were administered either parenterally or orally to animals with experimental renal hypertension, a marked and prolonged decline in blood pressure occurred. The administration of the antipressor substance by similar routes to a small group of patients with hypertension resulted in a decline in blood pressure. However, the authors emphasized the fact that it is unwise to draw any conclusions from such a small series of cases and preferred to wait until a much larger series of cases is studied.

There is no positive evidence to show that the kidney is concerned in the production of all types of hypertension. These experimental observations are not only of theoretical interest but also of great practical importance, for they have established on a firm basis the renal origin of hypertension and should stimulate, and in many cases have stimulated, intensive clinical study of every case of hypertension particularly from a urologic standpoint.

CLASSIFICATION OF NONNEPHRITIC DISEASES OF THE KIDNEY ASSOCIATED WITH HYPERTENSION

The following is a classification of nonnephritic diseases of the kidney which cause or are accompanied by hypertension, and in many instances, are amenable to surgical treatment. The nephritides associated with hypertension are purposely omitted. The important etiologic factor in each lesion is renal ischemia resulting from interference with renal circulation by the disease process. This may be brought about by intrinsic factors operating within one or both kidneys or by extrinsic factors usually affecting the main arterial supply of one or both kidneys. No attempt has been made to classify the specific causative lesions from the standpoint of their unilaterality or bilaterality, as this phase of the subject is considered in the subsequent discussion of the role of each causative lesion.

I. Inflammatory disease (acute and chronic
   - A. Pyelonephritis
   - B. Tuberculosis
   - C. Infections complicating other lesions; i.e., calculi, hydronephrosis, polycystic disease, etc.

II. Obstructive lesions
   - A. Hydronephrosis
   - B. Pyonephrosis
   - C. Nephroptosis

   } Associated with obstructive, inflammatory or neoplastic lesion in the lower urinary tract or genital tract

III. Vascular lesions
  A. Arteriosclerotic kidney
  B. Localized arteriosclerosis of renal arteries
  C. Arteriolosclerosis of kidney
  D. Thrombosis of large and small renal arteries with or without infarction
  E. Infarct of kidney
  F. Spasm of renal vessels
  G. Inflammatory or obliterative lesions of renal arteries and arterioles
    1. Endarteritis; i.e., obliterans type and syphilitic type
    2. Thromboangiitis obliterans
    3. Periarteritis nodosa
  H. Traumatic injuries of kidney, parenchyma, and vascular pedicle
  I. Compression of renal vessels by intrinsic or extrinsic lesions; i.e., tumors, aneurysms
  J. Miscellaneous lesions
    1. Thrombosis of abdominal aorta
    2. Coarctation of aorta
    3. Aneurysm of aorta, etc.
IV. Neoplasms of kidney and adrenals
  A. Kidney tumors in adults
  B. Kidney tumors in infants and children
  C. Adrenal tumors
V. Congenital renal anomalies
  A. Anomalies of kidney; i.e., form, structure, position, etc.
  B. Anomalies of blood vessels; i.e., course, position, size, and lumen
  C. Congenital cystic disease; i.e., polycystic disease

I. Inflammatory Lesions of Kidney Associated With Hypertension.—Prior to 1930 hypertension of renal origin was regarded as a relatively rare disease and was usually considered as limited to acute and chronic glomerulonephritis and a few other uncommon diseases of the kidney; i.e., polycystic diseases, nephrosclerosis, etc. However, since that time the prevailing concept that the vast majority of hypertension cases were of the essential (nonrenal) type has undergone a gradual but decided revision in the minds of most clinicians and even has been completely discarded by a few clinicians.

A. *Pyelonephritis.*—Of all the inflammatory diseases bearing some relation to hypertension, chronic pyelonephritis appears to be the one disease toward which most attention has been directed in recent years. Before attempting a discussion of the association or relation of hypertension to chronic pyelonephritis, it is important to have an accurate and clear conception of this pathologic entity inasmuch as considerable confusion and misunderstanding prevail in the literature regarding the exact definition and description of chronic pyelonephritis. This is evidenced by the numerous conflicting definitions which have been used, heretofore, synonymously and, too often, incorrectly; i.e., renal agenesis, aplasia, hypoplasia, or atrophy; atrophic pyelonephritis, nephrofibrosis, nephrosclerosis, etc.

One of the chief points of contention has been the exact pathologic significance and clinical interpretation of the various types of renal

atrophy. The need for a more descriptive and inclusive term than renal atrophy is quite obvious when one realizes that atrophy merely suggests a reduction in size of the organ and fails to take into consideration the etiology. Further, it is essential that one recognize the true nature of the atrophic kidney from the standpoint of its effect upon renal function, its relation to infection or obstruction in the urinary tract, its relation to hypertension before instituting a rational plan of treatment, surgical or otherwise, not only of the renal lesion, but also of the underlying factors or lesions in the urinary tract which may be responsible for its production.

Several writers have attempted to clarify and define the various types of renal atrophy. In the main, they have classified the cases into two main groups: (a) congenital atrophy, which is the result of a developmental defect in the metanephric mass; i.e., renal agenesis, aplasia, and hypoplasia; and (b) acquired atrophy, due to a disease process. Cumming and Schroeder employed the term nephrofibrosis for the latter group, which they defined as a "localized or diffuse destructive or degenerative condition of the kidney which may or may not have originated as an infective or infected embolic process but results in a decrease in the size of the organ due to fibroplastic proliferation." They classified the etiologic factors of "nephrofibrosis" as follows: (1) obstruction, (2) trauma, (3) postoperative, (4) infection, (5) calculosis, (6) idiopathic (atrophy of disuse). They distinguish nephrofibrosis from nephrosclerosis, the latter being considered as a degenerative vascular change in the kidneys associated with generalized vascular disease and having an entirely different etiology and symptomatology. I personally agree with this classification and definition but prefer the term chronic atrophic pyelonephritis as more descriptive and inclusive than nephrofibrosis.

As early as 1910, Longcope and McClintock mentioned the clinical relationship between chronic pyelonephritis and hypertension. Following this important contribution, interest appeared to lag, as evidenced by the fact that in 1930 Bell and Pedersen discussed the causes of hypertension and noted that there had been no reports of hypertension caused by pyelonephritis. However, interest has been revived in recent years, as attested by the studies and reviews published by Longcope, Butler, Crabtree, Weiss and Parker, McCann, Putschar, Kimmelstiel and Wilson, Braasch, and others. It is from their excellent contributions that much of the following information has been drawn.

In 1932 Staemmler collected 30 cases of pyelonephritis with contracted kidneys, marked elevation of blood pressure, and cardiac hypertrophy. In 1933 Longcope and Winkenwerder described 9 patients with supposed chronic nephritis with uremia, who at autopsy had a bilateral pyelonephritis, contracted kidneys, and irregularly dilated pelves. Although hypertension was present in 5 cases, the authors failed to emphasize chronic pyelonephritis as the cause of the hypertension.

In 1936 Kimmelstiel and Wilson studied the incidence of hypertension and renal insufficiency in 56 cases of pyelonephritis. Primary lesions in the genitourinary tract were present in 29 of these cases. They classified their cases in four groups: (1) acute focal nephritis (neither hypertension nor renal insufficiency); (2) acute diffuse pyelonephritis (13 cases; 9 died in uremia; hypertension in 4 cases); (3) chronic diffuse pyelonephritis (with focal or unilateral contraction of kidney; hypertension present in 6 of 9 cases; uremia cause of death in 3 hypertensive patients); (4) chronic diffuse pyelonephritis (26 cases; hypertension and uremia associated in 16; hypertension alone in 4; uremia alone in 6).

In 1937 Longcope reported the results of a continuous study of 22 cases of chronic pyelonephritis which terminated fatally. He observed that hypertension occurred in 50 per cent of the cases and was a late or terminal feature of the disease. He maintained that the hypertension could not be ascribed to a diminution of renal functional capacity inasmuch as several patients died of renal insufficiency without hypertension. He did not emphasize the vascular lesions of pyelonephritis or their relation to hypertension.

Weiss and Parker made an excellent and comprehensive clinicopathologic study of 100 cases of chronic pyelonephritis, and their findings confirm the clinical observations of Longcope. They have emphasized certain pathologic features of pyelonephritis whose morphologic and clinical significance has not been well recognized or fully appreciated. A summary of their most pertinent findings are herewith presented:

a. The structural characteristics of pyelonephritis are essentially the same regardless of the type of infection; i.e., hematogenous, urogenous, or lymphatic.

b. Pathologic changes involve the renal lymphatic and vascular systems as well as the nephron and interstitial tissue.

c. Pyelonephritis, particularly in the chronic and healed stages, is frequently associated with hypertension, and pyelonephritis is the causative lesion in at least 15 to 20 per cent of malignant hypertensive cases.

d. There is a relation between the severity and diffuseness of the vascular lesions of pyelonephritis and the arterial hypertension. Cases of severe hypertension showed changes characteristic of advanced hyperplastic arteriosclerosis, productive endarteritis, and necrotizing arteriolitis which are similar to those observed in malignant nephrosclerosis. The vascular changes and the renal functional damage are due to the same cause, but may be independent of each other.

e. The vascular changes of chronic pyelonephritis are restricted to the kidneys in contrast to the generalized changes observed in malignant hypertension.

f. Chronic or healed pyelonephritis rarely coexists with chronic glomerulonephritis; the former condition is more frequent than the latter.

g. Pyelonephritis may complicate polycystic disease, hydronephrosis, and tuberculosis. However, the vascular lesions characteristic of chronic pyelonephritis do not occur in tuberculosis or hydronephrosis uncomplicated by pyelonephritis.

Putschar has studied the histogenesis and morphologic findings in acute and chronic pyelonephritis. He pointed out that a chronic progressive type of pyelonephritis is not uncommon and that in the majority of such cases purulent exudate and abscess formation may be entirely absent. He maintained that the inflammation creeps along in the interstitial tissue and causes progressive fibrosis and scarring in the kidney areas. This process may be restricted to one portion of the parenchyma or involve the entire kidney; it may be unilateral or bilateral. Pyelonephritic contracted kidneys are observed more commonly in women than in men (3:1). In cases of unilateral contracted kidney, a marked compensatory hyperplasia occurs on the opposite side. Kimmelstiel and Wilson have described two types of glomerular lesion in chronic pyelonephritis. The first type, which is peculiar to this condition, is due to the extension of the interstitial inflammation to the glomeruli. The second is an "alterative" type of glomerulitis which occurs in the pyelonephritic contracted kidney as a manifestation of a generalized vascular disease. The latter type is independent of the former but is practically indistinguishable from the focal glomerulitis found in so-called essential hypertension of the benign or malignant type.

Peters and his associates have shown that not infrequently pregnancy may precipitate the hypertensive phase of pyelonephritis which, in turn, may initiate the eclamptic syndrome. Crabtree and Prien maintained that hypertension is not the ruler in severely injured kidneys due to pregnancy pyelonephritis, as they found hypertension in only 2 of 30 cases of severe bilateral pyelonephritis in pregnancy at from ten to eighteen years after initial injury. They considered that infectious injuries to the arteries of the cortex served as possible cause for setting in motion the requisite forces responsible for hypertension in these cases. They also emphasize the fact that in bilateral cortical necrosis of kidney, a frequent complication of pregnancy, a rise in blood pressure is seldom observed despite the fact that the patients excrete little or no urine for long periods of time, varying from six to twenty-five days.

In a subsequent five- to ten-year follow-up study of 45 patients with pyelonephritis of pregnancy, Crabtree and Reid noted that the prognosis was grave for patients with both toxemic and pyelonephritic injury as indicated by the fact that all 3 patients with both conditions had hypertension and 2 of these were dead five years after the injury. Elevations in blood pressure above 150/90 with evidence of renal insufficiency were found in 6 patients with pyelonephritis of pregnancy. Renal calculi were found in 5 patients. They maintained that pyelonephritis of pregnancy was a progressive disease in many cases. In a review of the previous two series of cases Crabtree concluded that a high percentage of pregnancy pyelonephritic cases show evidences of renal damage after five to eighteen years and that hypertension is not the rule in the same group of cases, as only 8 of 72 cases developed hypertension.

Weiss, Parker, and Robb maintained that the infection in pyelonephritis may heal but that the hypertension initiated by the inflammatory changes may continue to progress. While it is generally recognized that hypertension may develop before any evidence of renal insufficiency presents itself in cases of chronic pyelonephritis, the exact mechanism responsible for the increase in arterial blood pressure has not been clearly established. Weiss and Parker offered the following interesting explanation for the pathogenesis of hypertension in these cases; viz., (1) the chronic progressive inflammatory processes caused vascular changes within the kidney with resulting ischemia; (2) the renal ischemia tended to initiate the hypertension; (3) the hypertension in turn accentuated proliferative vascular changes by altering the permeability of the walls of the renal blood vessels; (4) the alteration of the permeability permitted certain substances to exude into the perivascular tissues which, in turn, aggravated proliferative processes in the blood vessels, thereby increasing the ischemia. Thus a vicious circle is set up.

Some writers have raised the objection that the hypertension is not always related to the chronic pyelonephritis in the above type of case but rather is the result of other causes or lesions which occur in the latter period of life and are not always discernible. However, such objections and claims are invalidated by the frequent reports of hypertension in infants and young adults with chronic pyelonephritis. In 1937 Butler emphasized the definite relation between chronic pyelonephritis and arterial hypertension in children. In a series of 15 cases of pyelonephritis in children, he observed hypertension in 8 cases and reported 2 cases of chronic unilateral pyelonephritis with hypertension in children whose blood pressure returned to normal after nephrectomy. The latter are the first recorded cases to substantiate the contentions that sustained hypertension in human beings may be due to chronic inflammatory disease of one kidney and that removal of the affected kidney results in cure. One of these cases was subsequently reported by Barney and Suby. Bothe and Patch and associates obtained good results in similar cases in young children treated by nephrectomy. Cases of unilateral chronic pyelonephritis with hypertension in adults, which have successfully been treated by nephrectomy, have been reported by Crabtree, Barney and Suby, Walters and Barker, Nesbit and Ratliff, Bothe, McIntyre, Schroeder and Fish, and Everett.

Schroeder and Fish reported 4 cases of arterial hypertension due to chronic pyelonephritis and treated by nephrectomy. Varying degrees of arterial and arteriolar changes were present in all kidneys removed in addition to the chronic inflammatory changes. The results varied; a marked improvement was noted in the patient in Case 7, who had a hypoplastic kidney with slight inflammatory and vascular changes; a slight improvement manifested by a temporary fall in blood pressure was obtained in the patient in Case 5, who had a unilateral pyelo-

nephritic contracted kidney following chronic pyelitis of childhood; no improvement occurred in the patient in Case 2, who had a contracted pyelonephritic kidney as a result of pyelonephritis of infancy and pregnancy and died of renal failure five months after nephrectomy; no improvement was noted in the patient in Case 4, who had arterial hypertension of nine years' duration and whose right kidney was removed for advanced pyelonephritic contraction and ptosis. In the last 3 cases advanced arteriolar sclerosis was present in the kidneys.

Everett reviewed the findings in forty-one consecutive nephrectomies and found extensive chronic pyelonephritis with severe vascular lesions in the smaller arteries and arterioles in 19 patients. In the latter group 6 patients had suffered from hypertension and only 3 had a reduction in blood pressure following nephrectomy. Walters and Barker reported 5 cases of unilateral chronic atrophic pyelonephritis associated with hypertension which were successfully treated by nephrectomy. In each case the blood pressure returned to normal limits following the operation. In each case pathologic studies of the diseased kidney showed extensive atrophy and scarring with marked thickening of the arterial walls in the scarred areas. In a series of 57 cases in which a diagnosis of chronic atrophic pyelonephritis was made urographically, an elevation of the blood pressure (i.e., in excess of 145 mm. systolic and 90 mm. diastolic) was noted in 26 cases (45.6 per cent). In a series of 24 cases in which the diagnosis was made from pathologic studies following nephrectomy, 15 cases (62.5 per cent) showed elevations in blood pressure.

Braasch observed 47 cases of hypertension in 180 cases of chronic pyelonephritis. Hypertension occurred more frequently in patients with marked pyelographic changes and in those with impaired renal function. Hypertension was found in 26 per cent of the patients with chronic pyelonephritis as compared with 20 per cent of controls in the same age group. He maintained that pyelonephritis served as an irritant to bring out a latent hypertension. He stated that pyelonephritis does not produce hypertension in an otherwise normal person.

Braasch, Walters, and Hammer reported preoperative hypertension in 20 of 43 patients treated by nephrectomy for primary atrophic pyelonephritis, an incidence of 46.5 per cent. The incidence of hypertension was decidedly lower in patients who had nephrectomy for pyelonephritis without atrophy or sclerosis. They studied the postoperative course of the blood pressure in 18 of 43 operative cases of atrophic pyelonephritis. They found that preoperative hypertension was present in 10 of these 18 patients and that following operation the blood pressure returned to normal in 7 patients and was not influenced in 3 patients. Of the 8 patients who had a normal blood pressure preoperatively, hypertension developed after operation in only 1 case. They observed that the percentage of cases in which blood pressure was permanently reduced after nephrectomy for atrophic pyelonephritis was far greater

than when nephrectomy was performed for any other type of renal lesion. They maintained that the widespread atrophy of the renal tissues and the sclerosis of the renal blood vessels were responsible for the hypertension. They noted that acute cortical renal infection or perinephritic abscess was seldom a factor in causing hypertension.

In their series of 7 cases of chronic pyelonephritis with hypertension treated by nephrectomy, Crabtee and Chaset observed a slight improvement in blood pressure in only 1 case.

CASE 1.—(G. U., No. 1284.) J. P., 52 years of age, white, male, married, grocer, was referred for a urologic study on June 1, 1932. He had been treated for "stomach trouble" for the past ten years. He had had cramplike pains in the lower left quadrant lasting from five to six hours and recurring at intervals of from three to four months. The pain was accompanied by nausea and vomiting, particularly after eating. There was a moderate amount of epigastric discomfort, belching, eructation, and heartburn. The patient gave a history of diurnal frequency every hour, nocturia two to three times, and hesitancy and burning. The patient had been subjected to repeated gastrointestinal studies, stomach analysis, proctoscopic examinations, etc.

Physical examination was essentially negative except for tenderness over the left kidney. The urine was negative except for an occasional pus cell. Cystoscopy and pyelography revealed a large hydronephrosis of the left kidney with an obstruction at the ureteropelvic junction. Intravenous phthalein had an appearance time from the right kidney of 4 minutes and from the left kidney of 8 minutes; a fifteen-minute collection from the right kidney was 18 per cent; from the left kidney, 2 per cent. Blood urea was 39 mg. per cent. On June 14, 1932, the left kidney was exposed under spinal anesthesia. An obstruction was found at the ureteropelvic junction, and the posterior peritoneum and descending colon were intimately adherent to the anterior surface of the distended extrarenal pelvis. A plastic operation was performed, removing an elliptical piece of tissue from the anterior and posterior surfaces of the renal pelvis and the stricture at the ureteropelvic junction was corrected by a Heineke-Mikulicz repair. The patient made an uneventful recovery and was discharged from the hospital in two weeks.

Prior to operation, the patient's blood pressure varied between 200 and 210 systolic and 110 and 120 diastolic. Following operation, his blood pressure fell to 170/110 and remained at this level for three months. Three months following the operation, the patient developed a sudden sharp pain in the operative area following the lifting of a very heavy object. Two days later he presented a soft fluctuating mass in the upper end of the wound. Cystoscopic and pyelographic studies at this time revealed a rupture of the left kidney pelvis with an accompanying perinephritic abscess. A nephrectomy was done on Sept. 20, 1932. Almost the entire left adrenal gland was removed also. The patient made an uneventful recovery. Following this operation the patient returned for observation for a period of three years, during which time there was no recurrence of his gastrointestinal symptoms. The blood pressure prior to his second operation was 166/96 and following operation it declined to 154/90. Blood pressure determinations, which were made at the time of each office visit, showed slight fluctuation at or about the latter level. On May 20, 1935, his blood pressure was 152/108.

The pathologic specimen disclosed a small pin-point perforation at the site of previous plastic operation at the ureteropelvic junction. Immediately surrounding this area was a localized abscess in the peripelvic fat. On gross and microscopic examination the kidney showed the characteristic changes of acute and subacute

pyelonephritis. There were moderately advanced sclerotic changes in the walls of the smaller vessels in the kidney and adrenal which were graded 2+.

CASE 2.—(G. U., No. 103221.) I. W. M., 50 years of age, male, white, married, high-school teacher, was referred to me for urologic study after admission to the Sinai Hospital on July 30, 1939, complaining of severe headaches. Both parents had died of "cerebral apoplexy" and one brother died at the age of forty-seven years of chronic nephritis. The patient had enjoyed good health until five months previously, when he developed severe occipital headaches accompanied by nausea and occasionally blurred vision. His condition became progressively worse with a gradual loss of strength and appetite and increased fatigability. For the past twenty years he has been troubled with diurnal frequency (every one to three hours) and pollakiuria, but no urgency, nocturia, dysuria, gross hematuria, retention, renal colic, or pain, etc. About fifteen months before he was examined for insurance and was told that his urine was negative and that his blood pressure was 150/100. On admission to the hospital blood pressure was taken daily and varied between 220 and 228 systolic and 116 and 124 diastolic. Ophthalmoscopic examination disclosed a marked tortuosity of the vessels with decided A-V nicking and many old hemorrhagic areas.

Physical examination was essentially negative except for the usual signs of cardiac hypertrophy and slight tenderness. The prostate was the seat of a mild chronic infection. The urine showed a specific gravity of 1.016, a faint trace of albumin, and on microscopic examination contained an occasional red blood cell and pus cell, and hyaline and granular casts. Blood studies revealed no anemia or leucocytosis. A combined phthalein test yielded a total of 38 per cent for two hours with the following successive half-hour estimations: 22, 10, 6, 0 per cent. Blood chemistry studies revealed the blood urea to vary between 78.09 and 97.07 mg. per cent; the blood chlorides between 412 to 433 mg. per cent; the CO_2 combining power between 36.5 and 56; uric acid, 3.8 mg. per cent, total protein, 6.98 mg. per cent. Urea clearance and concentration tests, which were done prior to hospitalization, showed impairment of renal function. A diagnosis of malignant hypertension was made, and the patient was referred for urologic study.

Intravenous urography revealed a normal kidney and calyces on the right but evidences of compression and distortion of the infundibular portions of the upper and middle major calyx on the left and incomplete filling of the terminal portions of these calyces. On the basis of these pyelographic changes, a presumptive diagnosis of (1) chronic pyelonephritis with cystic degeneration, (2) chronic nephritis with cortical cysts, or (3) solitary renal cyst or tumor was made and retrograde pyelography advised. The latter was done and compression changes involving the renal pelvis and upper and middle major calyces were found which were more suggestive of a solitary cyst than a neoplasm.

After lengthy discussion with the patient and his family physician, in which the dangers of operation were stressed and no hopes or promises of a cure were given, an exploratory operation through a left lumbar incision was performed on Aug. 1, 1939, under avertin-ether anesthesia. A large, round solitary cyst, measuring 8 cm. in diameter, was found on the posterior aspect of the kidney extending down to, but not invading, the pelvis. A resolving cortical abscess 1 cm. in diameter was present on the convex border near the lower pole of the kidney. An aberrant vessel entering the anteromedial aspect of the upper pole of the kidney was present. The main artery appeared to be slightly thicker than normal. It was impossible to remove the cyst without doing irreparable damage to the kidney. After much deliberation and consultation with the family physician, a left nephrectomy was done. Convalescence was complicated by a rather severe episode of hiccoughs occurring

on the first seven days following the operation, which was controlled by intravenous injection of sodium lactate solution. On the seventh postoperative day the patient fell out of bed during his sleep. Bleeding from muscles in the wound followed but was easily controlled by resuturing. The patient was discharged from the hospital on Aug. 15, 1939.

Following operation the blood pressure fell gradually to 140/98 on the fifteenth postoperative day and remained at this level for about six weeks. On Oct. 5, 1939, the blood pressure was 160/104, and the blood urea was 45.53 mg. per cent, but on Nov. 6, 1939, the blood pressure rose to 260/140, the blood urea to 67.11 mg. per cent, the urine showed 1+ albumin, many red blood cells, occasional pus cell, and a moderate number of hyaline and granular casts. The headaches recurred in a more severe and persistent form, accompanied by marked visual disturbances. There was a decided loss of strength, appetite, and mental instability, and the patient failed rapidly. He died on Jan. 12, 1940, four and one-half months postoperative. Unfortunately, permission for autopsy was not granted.

The pathologic diagnosis was (1) chronic interstitial nephritis, (2) chronic pyelonephritis, (3) solitary serous cyst, (4) cortical abscess, and (5) kidney infarcts. Advanced sclerotic changes in the walls of the smaller blood vessels were noted (grade 4+).

B. *Renal Tuberculosis.*—A cursory review of the more important contributions to the subject of renal tuberculosis fails to reveal any mention of a causal relationship between this disease and hypertension. The pathologic features of renal tuberculosis are too well known to warrant any detailed discussion in this article. Suffice it to say that the tuberculous process in the kidney may be classified into three groups; viz., the ulcerative, caseating, and sclerotic stages, of the disease. A prominent feature of each stage, particularly the early stage, is the fibrotic process which surrounds the tubercles and even may spread over a great part of the kidney and cause serious functional disturbance. Primary involvement of the blood vessels of the kidney rarely occurs, but vascular changes secondary to the fibrotic process may develop particularly in the late sclerotic stages of the disease. Hinman studied the vascular tree of renal caseocavernous tuberculosis by means of injection of barium sulfate and demonstrated that the tuberculous infection is not only responsible for changes in the vascular walls which impair the integrity and vitality of the kidney but also may provide the means of an obstruction with subsequent development of hydronephrosis. He pointed out that the secondary changes may almost completely mask the original picture in such cases. He also showed that the vessels in the immediate neighborhood of a tuberculous focus develop endarteritis obliterans which is clearly demonstrated by an area of noninjection in the barium sulfate preparation. The relation of such changes to hypertension has never been established. Weiss and Parker did not find any of the vascular changes, which are usually associated with chronic pyelonephritis and hypertension, in a small group of cases of tuberculosis uncomplicated by pyelonephritis. However, it is well recognized that tuberculous lesions of the kidney are frequently accompanied by a variety of secondary degenerative, inflammatory, or sclerotic changes of

a nontuberculous nature. Such secondary changes might conceivably lead to vascular changes within the kidney and subsequent hypertension. Since the occurrence of hypertension in renal tuberculosis is extremely rare, it is possible that the etiologic factor may be found in some specific or general condition outside of the kidney.

The only references to renal tuberculosis and hypertension which we have been able to find are the cases reported by Schroeder and Steele, Nesbit and Ratliff, Leadbetter, Kerr, Everett, Braasch, Walters, and Hammer, and Crabtree and Chaset. Volhard mentioned tuberculosis as a cause of hypertension but cited no cases. No history of operative treatment is recorded in the two cases of Schroeder and Steele. Nesbit and Ratliff's patient was a female 51 years of age with a right renal tuberculosis and hypertension of 180/100, which was successfully treated by nephrectomy. Following operation the blood pressure fell to 120/100 and had remained at that level at the time of the report fourteen months later. Pathologic study disclosed a far-advanced tuberculosis of the kidney with marked sclerosis of many arteries. No mention is made of a complicating pyelonephritis despite the fact that there appeared to be obvious clinical and microscopic evidence of same. The urine contained a few red blood cells, many pus cells, bacilli and streptococci, and on culture was positive for acid-fast bacilli. In the legend accompanying the photomicrograph of a section of the removed kidney, the following notation is found: "Showing marked sclerosis of the arteries, glomerular damage and inflammatory changes."

Leadbetter reported two cases of unilateral tuberculosis with blood pressures varying from 160/100 to 180/100. The blood pressure returned to normal in one case following nephrectomy. Kerr observed a case of hypertension associated with unilateral renal tuberculosis. Everett described a striking reduction in blood pressure from 160/115 to 115/74 following removal of a tuberculous kidney which showed, in addition to the typical tuberculous lesions, sclerosis of the smaller arteries and arterioles and hyalinized glomeruli similar to those seen in chronic pyelonephritis.

Braasch, Walters, and Hammer observed that the incidence of hypertension was lower in the presence of renal tuberculosis than in most other forms of surgical kidney. They found preoperative hypertension in 12 of 158 cases of renal tuberculosis, an incidence of 7.6 per cent. A follow-up study of this group revealed that of 11 cases with preoperative hypertension, the blood pressure after nephrectomy returned to normal in 7 cases and remained normal for less than a year, subsequently became elevated in 2 cases, and was uninfluenced in 2 cases. They believed that the age factor is important in explaining the low incidence of hypertension inasmuch as 132 patients (83.5 per cent) were less than 50 years of age. Furthermore, in their opinion vascular sclerosis is an uncommon pathologic feature of renal tuberculosis. They noted that a higher incidence of hypertension in the autonephrectomized type of renal tubercu-

losis occurred in 5 (13.5 per cent). The incidence of hypertension in cases with bilateral renal tuberculosis was not increased.

Crabtree and Chaset observed 1 case of tuberculous pyelonephritis with a preoperative hypertension of 154/105, and fourteen months following nephrectomy there was a reduction in blood pressure to 144/80.

CASE 3.—(Gyn., No. 4878.) A. B., 36 years of age, white, female, married, housewife, was admitted to the Sinai Hospital on Nov. 21, 1934, complaining of pain in the right upper quadrant and right lumbar region. The patient had been in good health until one year previously, when she developed pain in the right lumbar region and right upper quadrant radiating to the groin. The pain was unaccompanied by chills, fever, nausea, or vomiting. She also complained of diurnal frequency and nocturia. Hematuria was also present two months before for the first and only time. In the past year the patient had received cystoscopic treatments from another doctor with slight improvement.

Blood urea was 26.36 mg. per cent. Urine showed many pus cells. Combined intravenous phthalein yielded 60 per cent for the first hour and 15 per cent for the second hour. Cystoscopy and pyelography revealed a nonfunctioning pyonephrotic kidney on the right side. Cultural and staining studies failed to reveal tubercle bacilli in the urine. On Dec. 7, 1934, a right nephrectomy was done under ether anesthesia. The patient made an uneventful recovery and was discharged from the hospital on Dec. 24, 1934.

Blood pressures were taken daily prior to the operation and revealed a systolic pressure to fluctuate between 160 and 168 and the diastolic, between 90 and 100. Following operation the blood pressure gradually fell to 140/90 and remained at this level for the next two years, while she was under the observation of her family physician.

Pathologic diagnosis was (1) tuberculous pyonephrosis and (2) chronic recurrent pyelonephritis. Characteristic tubercles and abscesses were found as well as extensive degenerative and atrophic changes in the glomeruli, tubules, and interstitial tissue. The sclerotic changes in the walls of the smaller renal vessels were moderately advanced and were classified as 2+.

CASE 4.—(Gyn., No. 5651.) D. L., 21 years of age, white, female, married, housewife, was admitted to the Sinai Hospital on Oct. 14, 1936, complaining of frequency of urination. Her family history was negative. The patient had enjoyed good health until 1935, when symptoms of tuberculosis developed and she was sent to a sanatorium, where she spent six months and was discharged as an arrested case. For the past eight months the patient has complained of dull pain in the right lumbar region with diurnal frequency, burning and smarting on urination. In the past two months she has had an increase in symptoms, accompanied by pyuria and hematuria.

Examination revealed signs of a healed tuberculosis in both apices and tenderness over the right kidney. Urine showed 1+ albumin and many pus cells with clumps. Urinary sediment was stained for tubercle bacilli, but none were found. Blood urea was 31.06 mg. per cent. Cystoscopy and pyelography revealed numerous areas of hemorrhagic infiltration throughout the right half of the bladder. The right ureteral orifice had a typical "golf hole" appearance. Pyelography showed tuberculous ulceration of the upper major calyx of the right kidney. The left kidney appeared normal.

On Nov. 13, 1936, a right nephrectomy was done under ether anesthesia. The postoperative course was uneventful, and the wound healed per primam. Following her discharge from the hospital, the patient returned to the outpatient department

and received treatment for tuberculous cystitis with methylene blue irrigations after the method of Brodney.

Prior to her operation, her blood pressure was 148/86. Upon discharge from the hospital on Dec. 8, 1936, her blood pressure was 120/80. Subsequent blood pressure determinations were made at regular intervals in the outpatient department and the blood pressure did not exceed 120/80. The last blood pressure reading was taken on Oct. 15, 1940.

The pathologist's report indicated an advanced case of renal tuberculosis with localized abscesses involving the upper major calyx and diffuse involvement of remaining kidney tissue. Moderate endarteritis of the blood vessels throughout the kidney was noted (grade 1+).

CASE 5.—(G. U., No. 91269.) D. P., 24 years of age, white, male, married, clerk, was admitted to the urologic ward of Sinai Hospital on May 4, 1937, complaining of pain in his right flank. The family history was negative for tuberculosis. Six years before, the patient had complained of pain in his right flank and cystoscopy and pyelography revealed a bilateral renal tuberculosis accompanied by tuberculosis of the prostate. Hospitalization was advised but was refused by the patient who remained in bed at home for five months with definite improvement. In January, 1936, he contracted a gonorrheal urethritis which responded promptly to treatment. In March, 1936, he developed a bilateral tuberculous epididymitis with an accompanying hydrocele on each side. He was treated by ultraviolet ray to scrotum and frequent tapping of the hydrocele, but two persistent fistulas developed on the left side of the scrotum. In October, 1936, a bilateral epididymectomy was performed. Following this operation the patient developed signs and symptoms of pulmonary tuberculosis (confirmed by x-ray) and was sent to a state sanatorium for tuberculosis in December, 1936, where he remained until one week before this admission to the hospital. During his stay in the sanatorium, sputum examinations were consistently negative and repeated x-ray of the chest showed a rapid improvement. In the last two months he had developed pain in his left hip and complained of persistent scrotal fistula. He had no urinary symptoms.

Examination disclosed tuberculous involvement of the prostate, both seminal vesicles, both vasae, and the left testicle. Two fistulas were present on the left side of the scrotum. There was no tenderness over either kidney. A chronic tuberculous osteomyelitis of the middle phalanx of the right third finger was present. Slight tenderness was present over the left buttock, but x-ray failed to show any bone involvement in this area. The lungs showed no signs of active tuberculosis on physical and x-ray examinations. The urine was negative except for 60 to 70 pus cells per high power field. Repeated examination of the urinary sediment by acid-fast staining failed to reveal any tubercle bacilli. The blood urea varied between 15 and 26 mg. per cent.

On May 5, 1937, intravenous urography revealed a normal kidney pelvis on the left side but definite signs of tuberculosis in the upper major calyces of the right kidney. Both ureters appeared normal. On May 14, 1937, cystoscopy and pyelography were performed and disclosed marked tuberculous changes involving the upper and middle major and minor calyces and the pelvis of the right kidney. Urine from the right kidney was negative for tubercle bacilli and on culture grew colon bacilli.

On May 21, 1937, a right nephrectomy was done under spinal anesthesia. Despite the fact that about 5 cm. of ureter was removed and no drains were employed at time of operation, the patient developed a postoperative fistula in the lumbar wound which persisted after discharge from the hospital on July 17, 1937.

Prior to operation his blood pressure varied between 144 and 150 systolic and 92 to 96 diastolic. Following operation the blood pressure fell to 130/90 at time of discharge. On June 6, 1937, the consulting ophthalmologist reported marked congestion and tortuosity of the retinal veins, which were considered early hypertensive changes.

Following discharge from the hospital the patient returned to the sanatorium. The right lumbar persisted and drained a very slight amount of seropurulent material. Three scrotal sinuses were present and appeared to lead to the left testicle which was nodular. He was readmitted to the hospital on May 9, 1938. A left orchidectomy and excision of the fistulous tract was performed and primary wound healing obtained prior to his discharge on May 21, 1938. During this stay in the hospital his blood pressure never exceeded 122/78. Subsequent blood pressure determinations, taken by his family physician in the last two years, disclosed no elevation above 120/78.

Pathologic examination of the right kidney revealed a fairly well advanced tuberculous pyonephrosis. Caseating abscesses were found throughout the entire kidney but were more pronounced in the upper pole. Sclerotic changes (grade 2+) were found in the walls of some of the smaller blood vessels in the parenchyma.

C. *Chronic Infections of Kidney Complicating Other Lesions of Kidney.*—Hypertension has been described in individuals suffering from a variety of noninfectious diseases of the kidney; viz., renal calculi, obstructive uropathies, congenital anomalies of the kidney, etc. If a careful study of such cases were made, undoubtedly one would find in the majority of instances either a concomitant chronic infection or a history of an antecedent, intermittent, or recurrent infection whose occurrence has been forgotten by the patient and overlooked by the physician. Ample clinical evidence in support of this contention is found in the high incidence of chronic infection (pyelonephritis) in cases of renal calculi and obstructive uropathies, and in either case the end picture may be a contracted and scarred kidney of chronic pyelonephritis or a pyonephrotic kidney of varying size.

In view of the close relation between chronic pyelonephritis and calculi, one would expect to find reports of more cases of renal calculi accompanied by hypertension. The paucity of such reports may be due to any of the following reasons:

1. In the case of renal calculus, pain is an early but prominent feature of the disease which demands relief before infection or sufficient renal damage is permitted to occur and initiate those pathologic changes conducive to hypertension.

2. In chronic cases the presence of a calculus and infection is entirely overlooked or disregarded as the clinician's attention is focused on the hypertension. On the other hand, the urologist may overlook or fail to recognize the presence of hypertension, as his efforts are directed toward removal of the stone, eradiation of the infection, or alleviation of the pain.

3. In some cases the location of the calculus or the character of the infection associated with the calculus may produce pathologic changes

localized to a particular portion of the kidney with a minimum degree of renal damage.

4. A reluctance on the part of most physicians to report unusual case reports.

In their series of 56 cases of hypertension associated with renal diseases, Schroeder and Steele found 8 cases of renal calculi accompanied by hypertension and obtained a previous history of renal calculus or colic in 4 other patients. Maher and Wosika encountered 18 cases of renal calculi in their series of 101 cases of primary urinary tract pathology associated with hypertension. Longcope described a case of hypertension in an individual in whom a chronic renal infection accompanied a calculus imbedded in a calyx. Walters and Barker, Mulholland, and Nesbit and Ratliff reported cases of hypertension due to unilateral pyelonephritis secondary to renal calculi successfully treated by nephrectomy. Bothe reported a case of calculous pyonephrosis with hypertension which showed a slight improvement following nephrectomy.

It is also well to bear in mind that pathologic changes in or about the kidney other than pyelonephritis may develop and produce severe damage to the kidney parenchyma or to the vascular supply. A severe infection associated with a calculus in the kidney or ureter may cause extensive inflammatory or fibrotic changes in and about the kidney, pelvis, and ureter which may seriously interfere with the blood supply to these structures or act as an obstruction to outflow of urine. Such changes, which are prone to occur following the operative removal of stones from these structures as a natural sequela or as the result of faulty drainage, may lead to renal ischemia and subsequently influence the development of hypertension.

An example of the serious damage which may result from a ureteral calculus is demonstrated by the case reported by Hyman, and subsequently referred to by Oppenheimer, Klemperer, and Moschkowitz. A ureterolithotomy was performed in a male 30 years of age, which was followed two years later by pyelonephritis, hypertension, headaches, and retinal changes. Nephrectomy resulted in a cure. The striking pathologic finding was a marked sclerosis of the renal artery whose lumen was almost three-fourths occluded. Von Monakow also reported a case of ureteral calculus accompanied by an elevation in blood pressure to 170 mm. Hg which fell to 112 mm. after removal of the stone. Schroeder and Fish described a case of arterial hypertension which ran a malignant course and was associated with bilateral organic renal disease. The left kidney which was removed contained a calculus, chronic pyelonephritis and a hydronephrosis due to an aberrant vessel constricting the ureteropelvic junction. A slight hydronephrosis was present on the right. Nephrectomy did not influence the rapid downhill course. Marked arteriolar changes were present in the left kidney with slight

but similar changes in the right kidney. Everett reported a case of ureteral calculus accompanied by a pyelonephritic contracted kidney of long standing in which a reduction of hypertension followed nephrectomy.

Bothe noted a slight reduction in blood pressure following the removal of a calculous pyonephrotic kidney associated with an angulation of the upper ureter due to a fibrous band in a female, aged 53 years, who had had high blood pressure for years and suffered a paralytic stroke five months prior to operation. Her preoperative blood pressure ranged between 174 and 202 mm. systolic and 104 and 148 mm. diastolic, but following operation her general condition improved considerably and her blood pressure fell to 140/80 one week after discharge from the hospital.

Braasch, Walters, and Hammer observed hypertension in 161 cases (20.3 per cent) of 793 patients operated upon for stone; i.e., hydronephrosis with stone, stone with renal infection, stone without renal infection. They emphasized the important role of secondary infection in the production of hypertension in these cases which is substantiated by the fact that hypertension was present in 22.5 per cent of cases with infection as compared to 5.7 per cent without infection. They maintained that the deciding factor was not the degree of infection but the presence of vascular sclerosis and parenchymal atrophy. The incidence of hypertension in bilateral nephrolithiasis was no greater than in unilateral nephrolithiasis. It was interesting to note that in 8 (20 per cent) of 20 cases of atrophic pyelonephritis with hypertension, nephrolithiasis antedated the other conditions.

The postoperative course of the blood pressure was studied in 189 cases of which 111 had preoperative hypertension and 78 had a normal preoperative blood pressure. In the group of 111 cases with preoperative hypertension, the blood pressure returned to normal after operation in 25 cases, returned to normal for six months to two years but subsequently became elevated in 10 cases, and was uninfluenced in 76 cases. In the group of 78 cases with normal blood pressure before operation, hypertension developed following a conservative operation in 10 cases, several of whom required secondary nephrectomy before the blood pressure returned to normal.

CASE 6.—(Gyn., No. 1714.) S. D., 48 years of age, female, white, married, housewife, was referred to me for urologic study on April 10, 1939. The family history was unimportant. She had enjoyed good health until thirteen years previously, when she developed a right renal colic which recurred at intervals of from one to three months until November, 1938, when a urologic study was done elsewhere and a diagnosis of right renal calculus was made. The calculus was removed by operation. In January, 1939, the patient developed signs and symptoms of acute infection of the right kidney and bladder which had persisted to date despite treatment with various drugs; i.e., mandelic acid, pyridium, sulfanilamide, etc. In the last month she had severe pain localized to the right kidney area accompanied by chills, fever, nausea, vomiting, urinary frequency, burning, pyuria, etc. The

patient also complained of frequent headaches and dizzy spells in the three or four months before admission. She stated that she had been treated for "high blood pressure" the past three years.

Examination disclosed tenderness over the right kidney with a positive right ureteral point. Blood pressure varied between 188/100 and 210/110. Cystoscopy and pyelography were performed. A differential phthalein revealed appearance time from the right kidney to be 4 minutes as compared to three minutes from the left. Fifteen-minute collections from kidney showed the right kidney to be 8 per cent and the left kidney, 20 per cent. A diagnosis of staghorn calculus of the right kidney with chronic recurrent pyelonephritis (*Bacillus coli*) was made. There was an abnormal angulation at the right ureteropelvic junction which probably developed after previous operation and was responsible for the recurrent stone formation and the persistence of the renal infection.

On Apr. 25, 1939, a right nephrectomy was done. The patient made an uneventful recovery and was discharged from the hospital on May 20, 1939. During the last week of her hospital stay the blood pressure varied between 124 and 138 systolic and 60 to 70 diastolic. On Feb. 21, 1940 (ten months after operation), the blood pressure was 152/86, and on May 29, 1940 (thirteen months after operation), 158/92.

The pathologic diagnosis was (1) chronic pyelonephritis, (2) renal calculus, and (3) kidney infarcts. A marked thickening of the walls of the smaller blood vessels was noted with occasional obliteration of some arterioles. The changes were graded 2+.

CASE 7.—(G. U., No. 1681.) J. C., 49 years of age, male, white, married, salesman, was admitted to the Sinai Hospital on Apr. 23, 1935, complaining of pain in his left kidney region and hematuria of two weeks' duration. On April 1, 1932, he had had a left nephrolithotomy for renal calculi. Following this operation, he was asymptomatic until 2 weeks before this admission.

Physical examination disclosed chronic bronchitis and bronchiectasis in addition to tenderness over the left kidney. His blood pressure on admission was 168/88, and prior to operation varied between 166 and 174 systolic and 84 and 92 diastolic. The urine revealed 50 pus cells, occasional red blood cell per high-power field, and colon bacilli. The blood urea nitrogen was 15.12 mg. per cent and combined phthalein excretion was 50 per cent for the first hour and 10 per cent for the second hour. Ophthalmoscopic examination was not done. Cystoscopy and pyelography revealed a nonfunctioning left kidney containing a large staghorn calculus. Phthalein excretion from the right kidney was 30 per cent in fifteen minutes but none from the left kidney in same time interval.

On Apr. 26, 1935, a transperitoneal left nephrectomy was done; the patient made an uneventful recovery, except for hiccoughing which was successfully combated and for a disruption of the wound requiring secondary closure. He was discharged on June 11, 1935 (forty-seventh postoperative day). Prior to discharge the blood pressure was 140/80. The patient returned for periodic examination to his family physician, who reported that his blood pressure taken on July 15, 1935, was 132/80 and had remained at about the same level during the next three years that he was under observation.

The pathologic diagnosis was (1) chronic pyelonephritis and (2) nephrolithiasis. In addition to the characteristic lesions of chronic pyelonephritis, slight endarteritic changes were noted in the walls of the smaller blood vessels which were graded 1+.

CASE 8.—(G. U., No. 1668.) J. R., 52 years of age, white male, married, bartender, was first seen in my office on Feb. 5, 1939, complaining of pain in his right

lumbar region for the previous ten days. Family history was negative. He had enjoyed good health until 1930, when he had a stone removed from his right kidney. For the previous three years he had been receiving treatments for a chronic prostatitis. The patient stated that he had been treated for the usual symptoms of "high blood pressure" for the past two years. At present he complained of dull intermittent pain in the right kidney region, urgency, frequency, nocturia. There was no hematuria or colic.

Examination disclosed tenderness over the right kidney, anteriorly and posteriorly, and a mild degree of chronic prostatitis. Ophthalmoscopic examination revealed moderately advanced changes in retinal vessels indicative of hypertensive disease. Blood pressure was 192/110. Voided specimen of urine showed a trace of albumin and microscopically 8 to 10 pus cells per high-power field. Cystoscopy and pyelography revealed a group of three small stones in the lower major calyx of the right kidney which showed the typical pyelographic changes characteristic of chronic atrophic pyelonephritis. The right ureter appeared to angulate at the ureteropelvic junction. Fractional differential phthalein test revealed the appearance time from the right kidney to be 18 minutes and from the left kidney to be 3 minutes; a fifteen-minute collection from the right kidney was 0 and from the left kidney was 18 per cent. A diagnosis of right chronic atrophic pyelonephritis with nephrolithiasis and hypertension (Goldblatt type) was made.

The patient was admitted to the Sinai Hospital on March 13, 1939. Blood pressure determinations were done daily and ranged between 192 and 196 systolic and 110 to 114 diastolic. Two electrocardiographic examinations were made and were reported negative. On March 13, 1939, right nephrectomy was performed. His blood pressure fell to 162/100 on March 22, 1939, and to 158/100 on March 27, 1939, when he was discharged from the hospital.

The wound continued to drain a slight amount of seropurulent material, and the patient was readmitted to the hospital. The source of the persistent infection in the wound was found to be in the right ureter and on June 9, 1939, a right ureterectomy was performed and the wound healed per primam. He was discharged from the hospital on June 23, 1939, at which time his blood pressure had fallen to 134/80. The patient subsequently reported to the outpatient clinic at regular intervals, and blood pressure determinations were made which varied from 134 to 140 systolic and 80 to 110 diastolic. The last recording was 140/108 on April 13, 1940 (thirteen months after nephrectomy).

The pathologic diagnosis was (1) chronic pyelonephritis (2) renal calculi, and (3) renal infarcts. Typical changes of chronic pyelonephritis were present throughout the kidney. Hyalinization of the glomeruli was especially marked. Sclerotic changes in the walls of the cortical vessels were rather striking for many vessels showed complete obliteration and fibrotic replacement. The vascular changes were graded 2+.

CASE 9.—(Gyn. No., 99629.) R. C., 38 years of age, female, white, married, housewife, was admitted to the Sinai Hospital on Dec. 3, 1938, with a complaint of pain in her right lumbar region of two months' duration. Family and past histories were negative, except that the patient had been treated in the psychiatric and endocrinological outpatient departments in the previous five years for various physical and mental maladjustments. Five days before admission she had had an attack of right renal colic with hematuria which persisted until admission to the hospital.

Examination revealed an obese female of low mentality with marked spasticity, rigidity, and tenderness over the right kidney. A medical consultation was obtained, and the following diagnosis was made: (a) hypertensive cardiovascular disease, (b) renal calculus with polyglandular dyscrasia (moron), and (c) moron.

The eye grounds were reported negative. Her blood pressure was taken daily for the first week and varied between 160 and 164 systolic and 100 and 104 diastolic. The urine was negative except for many pus cells and red blood cells. Blood urea was 21.57 mg. per cent. Basal metabolism was 9. Cystoscopy and pyelography disclosed a large calculous pyonephrotic right kidney. Fractional differential phthalein showed a normal appearance time from each kidney, but the 15-minute excretion from the right kidney was 3 per cent against 15 per cent from the left kidney.

On Dec. 15, 1938, a right nephrectomy was done. The patient had an uneventful recovery and was discharged on Jan. 8, 1939. Following operation the blood pressure fell to 120/64 and prior to discharge from the hospital was 120/80. The patient returned to the outpatient clinic for observation where the following blood pressure determinations were made: May 2, 1939 (four and one-half months postoperatively), 170/120; May 16, 1939 (five months postoperatively), 180/110; Aug. 2, 1939 (eight months postoperatively), 150/98; Oct. 10, 1940 (twenty-two months postoperatively), 146/100. On May 8, 1939, ophthalmoscopic examination revealed no signs of nephritis or hypertension.

The pathologic diagnosis was (1) pyonephrosis and (2) multiple renal calculi. Histologic studies revealed changes characteristic of a well-advanced pyonephrosis; viz., abscess formation, fibrosis, granulation tissue, round-cell infiltration, degenerative and atrophic changes in the glomeruli and tubules, and hemorrhagic infiltrations. Sclerotic changes in the walls of the smaller renal vessels were readily discernible and graded 1+.

CASE 10.—(Gyn., No. 8076.) R. G., 51 years of age, white female, married, housewife, was admitted to the Sinai Hospital on Nov. 9, 1938, complaining of pain in the left kidney region. The family history was unimportant. She had had an appendectomy and suspension of the uterus in 1923. In May, 1928, she was admitted to the hospital and treated for hypertension and migraine, during which time the blood pressure varied from 218/130 to 162/102. In February, 1934, the patient had a right pyelolithotomy performed.

For the past two years the patient had complained of dizziness, headaches, nausea, vomiting, paroxysmal nocturnal dyspnea, loss of weight, oliguria, nocturia, and frequency. Physical examination revealed hypertensive cardiovascular disease, cardiac hypertrophy, and a hernia of the right kidney incision. Ophthalmoscopic examination revealed moderately advanced hypertensive changes of the retinal arteries.

Cystoscopy and pyelography revealed a calculous pyonephrosis on the right. The fractional phthalein showed 2 per cent excretion from the right kidney and 18 per cent from the left kidney in fifteen minutes. Urine showed a faint trace of albumin and microscopically a few pus and red blood cells and rare cast, and many colon bacilli. The blood urea was 45.53 mg. per cent. Combined phthalein test showed 20 per cent excretion for the first hour and 10 per cent for the second hour.

On Nov. 12, 1938, the right kidney was removed. During the convalescence, the blood pressure fell from the preoperative level of 220/120 to 140/90. The patient was discharged on Dec. 4, 1938.

Following discharge from the hospital, the patient was observed in the outpatient department. Her blood pressure gradually increased above the preoperative level, and on March 12, 1939, the reading was 220/124. She was readmitted to the Sinai Hospital on Dec. 20, 1939, with typical signs and symptoms of an advanced hypertensive cardiovascular disease with marked impairment of renal function. All of the clinical symptoms noted above were increased in severity. Her blood pressure on admission and for several days thereafter varied between 230 and 245 systolic and 126 to 135 diastolic. Ophthalmoscopic examination showed

a marked increase in the extent and severity of the hypertensive changes in the retinal arteries. Plain plate of the genitourinary tract showed no radiable shadows, but there was a decided decrease in the size of the left kidney. The blood chemistry at this time showed serum protein, 6.33 mg. per cent; albumin, 3.94 mg. per cent; globulin, 2.41 mg. per cent; blood chlorides, 536 mg. per cent; urea, 218.19 mg. per cent; creatinine, 3.99 mg. per cent; calcium, 11 mg. per cent; and PO_4, 3.6 mg. per cent. She had a marked anemia with hypochromia with a hemoglobin of 10 Gm. (58 mg. per cent); white blood count was 7,800; combined phthalein showed total excretion of 5 per cent for the first hour and 0 per cent for the second hour. With rest in bed and other supportive measures, including frequent intravenous injections of glucose, there was a slight reduction in blood pressure to 210/120. However, in view of extensive hypertensive cardiovascular damage and seriously impaired renal function, the prognosis was poor.

II. Obstructive Lesions of the Upper Urinary Tract.—In the latter half of the nineteenth century, a period in which accurate blood pressure determinations were not available, one finds an occasional reference to the occurrence of cardiac hypertrophy (i.e., hypertension) in cases of obstructive lesions of the genitourinary tract. This pathologic complication was first pointed out by Friedreichs in 1853 in a case of hydronephrosis and was subsequently observed by Potain in 1875 in prostatic enlargement, by Cohnheim in 1877 in bilateral ureteral obstruction due to a huge vesical calculus, by Strauss in 1882 in ureteral obstruction resulting from a carcinoma of the uterus, and by Weill in chronic cystitis with ascending infection of both kidneys.

In the past twenty years urologists have recognized the frequent occurrence of hypertension in various obstructive lesions of the urinary tract. In 1906, Passler reported a case of anuria of twelve days' duration, resulting from partial occlusion of both ureters by infiltrations from a carcinoma of the cervix. In 1911, Braasch described three cases of carcinoma of the uterus with infiltration of the broad ligaments and compression of both ureters. During the periods of anuria, the blood pressure rose sharply but fell to normal when the urinary obstruction was relieved by ureteral catheterization. The beneficial effects of preliminary bladder drainage in cases of hydronephrosis with hypertension due to prostatic hypertrophy was first pointed out by von Monakow and Mayer in 1918, and subsequently in 1920 and 1923 by O'Connor, and in 1936 by Ritch. In 1933, Abeshouse pointed out that in patients with acute retention of urine, the blood pressure, especially the systolic, is frequently elevated and gradually recedes with the institution of decompression and drainage. Abeshouse also stressed the fact that not all hypertensive patients had a lowering of the blood pressure upon relieving the obstruction, but the number of patients so developing a lowering of blood pressure suggested prostatic obstruction as one of the causes of hypertension.

The occurrence of hypertension in obstructive lesions of the upper urinary tract was investigated in 1917 by Lohlein, who described 2

cases of hydronephrosis accompanied by elevations in the blood pressure as high as 210/140, and in 1936 by Ritch, who described the beneficial effects of conservative urologic treatment in 5 cases of hydronephrosis due to various causes; i.e., ureteral strictures, ureteral kinks, ptosis, etc. Fishberg noted a marked reduction in hypertension following the use of an indwelling catheter in a case of tabetic paralysis of the bladder.

The significance of hydronephrosis as an etiologic factor in the production of hypertension is forcibly brought out by the recent statistical studies on the incidence of the various genitourinary lesions in cases of essential hypertension. In the 101 cases reviewed by Maher and Wosika, the frequency of primary obstructive lesions was as follows: prostatic obstruction, 31 cases; prolapse of uterus with hydronephrosis, 7 cases; diverticula of bladder, 5 cases; urethral stricture (male), 4 cases; carcinoma of bladder with ureteral obstruction, 2 cases; bladder stone, 1 case; and vesicovaginal fistula, 1 case. Schroeder and Steele demonstrated the presence of some primary abnormality in the urinary tract by intravenous urography in 50 of 71 cases of essential hypertension. In 36 cases the lesion was either a unilateral or bilateral hydronephrosis due to various types of obstruction. Oppenheimer, Klemperer, and Moschkowitz noted the occurrence of hypertension in 21 (32 per cent) of 66 cases of unilateral hydronephrosis or chronic pyelonephritis; the latter grouping was made because of the frequent association of the two lesions.

A. *Hydronephrosis.*—In a discussion of the pathogenesis of hypertension in obstructive lesions of the urinary tracts, we are not particularly concerned with the site or cause of the obstruction, for the effect on the upper urinary tract is practically the same in all instances. Urologists are familiar with the clinical and pathologic changes produced by simultaneous complete or partial obstruction of one or both ureters. However, the clinician, in the absence of roentgenologic and urologic investigation, may easily confuse the picture with chronic nephritis. The clinical diagnosis may be further complicated by presence of infection which may overshadow the effects of obstruction. This is particularly true in the case of chronic bilateral ureteral obstruction of moderate degree as pointed out by Scholl. He has also emphasized the fact that extensive destruction of the renal parenchyma is rarely caused by infection but is usually accompanied by some degree of obstruction in the urinary tract.

We are greatly indebted to Hinman for his comprehensive studies on the pathogenesis of hydronephrosis. He has employed the term hydronephrotic atrophy to denote the usual changes of pelvic dilatation and parenchymal atrophy following any type of urinary obstruction and considered it to be essentially a pressure and anemic atrophy. He differentiated this type from (a) primary atrophy in which the atrophy occasionally develops following a complete obstruction without dilatation

of the pelvis and tubules of the kidney; and (b) secondary atrophy in which changes due to infection or disuse are superimposed upon the above two types. In the development of hydronephrotic atrophy, four factors are involved; viz., pressure, anemia, degeneration, and disuse. Pressure is undoubtedly the primary factor, but anemia or ischemia plays the most important role once the process is initiated.

By studying the injected arterial tree, Hinman demonstrated that in hydronephrosis the circulatory changes are produced by mechanical displacement acting by compression or stretching according to the course of the vessels in relation to the direction of the pressure. As the pressure from the distending pelvis is transmitted to the parenchyma, the larger vessels become attenuated by stretching and a diminution of the flow of blood to and from the cortex ensues with a resulting partial anemia of the cortical parenchyma. The latter changes tend to lessen the normal tissue tone and favor a relaxation which is conducive to further changes by the process of distention.

The effect of this partial ischemia upon the development of hypertension is not known, but judging from the absence of hypertension in the vast number of cases of uncomplicated hydronephrosis, one may infer that there is little clinical evidence of such a relation. However, when the pathologic process of pressure and atrophy advance to the stage of renal insufficiency or when infection is superimposed, the likelihood of hypertension's developing becomes greater. Many of the obstructive uropathies, irrespective of the site or degree of the primary obstruction, are accompanied by pyelonephritis and calculi which have been shown to have a close etiologic relation to hypertension.

B. *Pyonephrosis.*—Some degree of infection usually occurs in practically every case of advanced hydronephrosis. The symptoms resulting from such an infection may be so severe or annoying that urologic investigation is instituted and a hitherto unsuspected and infected hydronephrosis revealed. Infection is particularly prone to occur in cases of hydronephrosis caused by calculi in the renal pelvis. The pathology of an infected hydronephrosis is essentially a pyelonephritis involving the pelvic mucosa as well as the parenchyma. The infectious process may spread and cause extensive suppurative changes in the parenchyma, producing a pyonephrosis.

Quinby reported a case of severe hypertension (systolic pressure of 250 mm. Hg) in a boy 14 years of age, caused by bilateral hydronephrosis and chronic pyelonephritis. Following the removal of a severely damaged kidney, the patient remained free from hypertension for ten years, but the following year the hypertension recurred. Hinman observed a similar case in a boy of 18 years of age, who had a systolic pressure of 218 mm. and died of uremia without any operation. Fishberg described a case of congenital bilateral hydroureter and hydronephrosis caused by a congenital valvular obstruction in the urethra and

accompanied by hypertension. I have encountered a similar case in in a 19-month-old boy, whose blood pressure before cystoscopic excision of the valves and left nephrectomy was 128/85 and during the period of postoperative convalescence fell to 108/65. Unfortunately a follow-up study of the blood pressure could not be obtained as the boy's parents moved to a distant city and could not be contacted. Relatives informed me that the boy has shown a remarkable improvement two years later. This case is not included in Table III.

Morton observed a marked fall in blood pressure following the removal of a hydronephrotic kidney caused by an anomalous blood vessel. Similar results have been obtained by Ritch, Nesbit and Ratliff, and Bartels and Leadbetter. Everett reported three interesting cases of hydronephrosis in whom a reduction in hypertension followed operation: (1) a colored female, aged 26 years, who had a large fibroma enucleated from the left iliac fossa, and ligation of the left ureter performed one year prior to the left nephrectomy for hydronephrosis complicated by chronic pyelonephritis; (2) a female, aged 37 years, who had a left nephrectomy for hydronephrosis with an old pyelonephritis and extensive atrophy of the left kidney and marked vascular sclerosis; and (3) a female, aged 36 years, who was subjected to a ligation of an aberrant vessel and resection of a large extrarenal pelvis in a case of a large hydronephrosis produced by obstruction of the ureteropelvic portion of the ureter by the aberrant vessels.

Bothe reported a case of hypertension (174/120) in a 3-year-old boy associated with bilateral hydronephrosis (more marked on the left) and complete stenosis of the left ureteral orifice. Following a suprapubic operation in which the left ureteral orifice was incised and the lower ureter freed, the blood pressure was greatly reduced (114/54).

Braasch, Walters, and Hammer observed a low incidence of preoperative hypertension; viz., 51 cases (13.7 per cent) in a series of 372 cases of hydronephrosis without stone. Hypertension occurred in only 7.7 per cent of patients under 50 years of age as compared with 38.9 per cent of patients over 50 years. The size of the hydronephrotic sac and the degree of pyelectasis did not appear to be factors in the production hypertension. They believed that the deciding factors were the resulting sclerotic and atrophic changes in the renal parenchyma. They studied the postoperative course of the blood pressure of 73 patients operated upon for hydronephrosis without stone. In this group 29 had hypertension preoperatively, and following operation, the blood pressure returned to normal in 10 cases (34.4 per cent) and remained so for from one to five years. Eight of these patients had a nephrectomy and two, a conservative operation. The hypertension persisted in 16 of the 29 cases treated by nephrectomy. In 42 cases the blood pressure was normal before and after operation, and in 2 other cases the blood pressure was normal before operation, but following operation hypertension developed. The preoperative hypertension, which

was present in 4 cases of bilateral hydronephrosis, was not affected by surgical drainage. However, hypertension developed in 2 cases of bilateral hydronephrosis in which one kidney was suddenly occluded, and following renal drainage, the blood pressure returned to normal in one case.

CASE 11.—(G. U., No. 1383.5.) J. B., white, male, 8½ years of age, was admitted to the surgical pediatric ward of the Sinai Hospital on May 3, 1933, complaining of pain in the right half of the abdomen of fourteen hours' duration. His family and past histories were essentially negative. About five days prior to admission to the hospital, the patient had a sore throat which cleared up with usual family remedies. On the morning of admission, the patient complained of dull pain in the right half of his abdomen, accompanied by nausea but no vomiting. His mother gave the patient a dose of epsom salts and later applied an ice bag to the right abdomen. Since pain persisted the mother brought the child to the hospital. She stated that two years before the patient had had a similar episode of pain in his right abdomen which persisted for one week and subsided with ice bags.

Examination disclosed a moderately distended abdomen with marked tenderness over the entire right upper and lower quadrants with a round tender mass about 10 cm. in diameter in the right upper quadrant. Leucocyte count was 8,000 with 76 per cent polymorphonuclear cells. The urine was negative except for an occasional pus cell. After much deliberation and consultation between the surgical and pediatric consultants, a tentative diagnosis of intussuception producing an incomplete intestinal obstruction was made in full cognizance that the laboratory findings did not support or confirm such a diagnosis. Exploratory laparotomy was performed, no intraperitoneal pathology was found, and a normal appendix was removed. The right kidney fossa was found to be occupied by a soft, fluctuant, cystic mass about 12 cm. in diameter, which was considered to be a multilocular pyonephrotic kidney.

On May 16, 1933, the patient was transferred to the urologic service. Cystoscopy and pyelography revealed a nonfunctioning multilocular pyonephrotic kidney on the right. The blood urea varied between 32.36 and 39.55 mg. per cent. A combined phthalein test showed 50 per cent excretion in the first hour and 25 per cent in the second hour. On June 16, 1933, a right nephrectomy was done. The operative specimen showed a large multilocular pyonephrotic kidney with a dense stricture of the ureter about 1 cm. below the ureteropelvic junction. The patient made an uneventful recovery. He was discharged from the hospital on June 28, 1933.

During his stay in the hospital a daily blood pressure record was kept. Prior to nephrectomy the blood pressure varied from 140/84 to 160/100. Following nephrectomy the blood pressure fell to 135/80. He was followed in the outpatient clinic for several years. The blood pressure gradually diminished to 120/80. The last blood pressure was recorded on Oct. 17, 1940, as 120/82.

The pathologic diagnosis was (1) multilocular hydronephrosis and (2) chronic pyelonephritis. Numerous areas of diffuse and focal leucocytic infiltrations were found scattered throughout the kidney parenchyma in addition to atrophic and degenerative changes in the tubules and glomeruli. The vascular changes were of a relatively mild degree (grade 1+).

CASE 12.—(G. U. No. 1945.) C. J., 56 years of age, white, married, male, iron and steel worker, was admitted to the Sinai Hospital on June 30, 1936, for pain in his left kidney region and hematuria. His family and past histories were unimportant. He had had left renal colic four weeks previously and had noticed blood in his urine on several occasions thereafter.

Physical examination was essentially negative except for tenderness in the left kidney region, cardiac hypertrophy, and hypertension (180/120). Unfortunately an ophthalmoscopic examination was not done. Urine examination disclosed 2+ albumin with 8 to 10 pus cells and 10 to 15 red blood cells per high-power field. Blood urea nitrogen was 24.64 mg. per cent. Cystoscopy, pyelography, and a differential phthalein test were performed and a diagnosis of nonfunctioning left pyonephrosis was made. On July 1, 1936, a left nephrectomy was done and the patient made an uneventful recovery, being discharged from the hospital on the twelfth postoperative day, when the blood pressure was 140/90.

The patient was under observation for the next ten months. The red and white blood cells disappeared from the urine, likewise the albumin. His blood pressure varied between 140 and 144 systolic and 90 and 92 diastolic. The patient was lost sight of until Oct. 13, 1940, when he reappeared for examination. The blood pressure was 170/110. The urine gave a positive test for albumin and on microscopic examination showed no red blood cells or pus cells but an occasional hyaline cast. Ophthalmoscopic examination revealed dilation and tortuosity of the retinal vessels. The patient stated that in the past six months he had been troubled with headaches, weakness, dizzy spells, and dyspnea.

The pathologic diagnosis was (1) pyonephrosis and (2) chronic pyelonephritis. Characteristic degenerative changes, such as fibrosis, necrosis, abscess formation, hyalinization, acute and chronic inflammatory infiltrations, etc., were found throughout the kidney. The large renal vessels at the hilum were thickened and the smaller vessels throughout the kidney parenchyma showed chronic degenerative changes in their walls varying from slight fibrosis to complete obliteration (grade 3+).

CASE 13.—(G. U., No. 1175.5.) M. K., 51 years of age, white, male, married, tailor, was admitted to the urologic ward of the Sinai Hospital on Feb. 9, 1932. In November, 1931, he had developed signs and symptoms of a stone in his right kidney, and a right nephrolithotomy was performed. The patient made an uneventful recovery except for a small fistula, which was present at the time of this admission to the hospital. He also complained of urgency, frequency, and burning. He had gained 20 pounds in weight. The patient was also treated for diabetes.

Physical examination was essentially negative except for tenderness over the right upper quadrant and right lumbar region. A small fistula was present in the upper end of the lumbar incision. Combined intravenous phthalein yielded 45 per cent for the first hour and 10 per cent for the second hour. Urine showed a trace of albumin and 1+ sugar and an occasional pus cell. Blood urea was 35.95 mg. per cent, and his blood sugar was 121 mg. per cent. Cystoscopy and pyelography revealed a nonfunctioning pyonephrotic kidney on the right side. On Feb. 16, 1932, a right nephrectomy was done under spinal anesthesia. The patient made an uneventful recovery and was discharged from the hospital on Mar. 8, 1932.

Prior to operation his blood pressure varied between 184 and 188 systolic and 110 and 114 diastolic. Following operation the blood pressure gradually fell to 152/92 prior to discharge from the hospital. For the next two years he returned to the outpatient department for observation and his blood pressure declined to 142/90 and remained at that level.

The pathologic diagnosis was pyonephrosis. Numerous recent and old abscesses were scattered throughout the scarred kidney. Several infarcts of varying size were present. Sclerotic changes in the walls of the smaller renal vessels were quite marked (grade 2+).

C. *Nephroptosis.*—It is highly probable that in cases of hydronephrosis associated with acquired nephroptosis, the development of partial

renal ischemia may be considerably influenced by other vascular changes incidental to the nephroptosis. These vascular changes include (a) elongation, narrowing, or compression of renal vascular pedicle resulting from traction by the abnormally mobile or prolapsed kidney; and (b) compression or constriction of the vascular pedicle as a result of renal torsion, ureteral kinks, fibrotic bands, adhesions, or aberrant vessels, which are the usual pathologic conditions associated with nephroptosis. The effect of these vascular changes upon the intrinsic circulation of the kidney may take place long before the intrarenal circulation changes caused by the hydronephrotic atrophy are manifested. It is only within the past two years that methods have been devised which enable us to determine the extent or effect of these primary vascular changes of nephroptosis upon the renal circulation and function. Smith and his colleagues have described an inulin clearance test which serves to determine the glomerular filtrate rate, while White and Rolf utilized a diodrast clearance test for the determination of the total renal plasma flow.

McCann and Romansky have recently studied the relation of orthostatic hypertension to nephroptosis by means of erect and recumbent pyelograms and by comparing the effect of posture on the blood pressure, on the glomerular filtration rate, and on renal blood flow. They found that in some instances of nephroptosis the erect posture may cause an orthostatic hypertension with diminution of total renal blood flow and relative constancy of glomerular filtration. They explained these findings; viz., (1) erect posture causes some slight interference with the afferent blood supply of the kidney which leads to the production of renin, and (2) the renin in turn acts to constrict the vasa efferentia in both kidneys which results in a decrease in the total renal blood flow without any appreciable effect on the glomerular filtration rate. They reported 5 cases of orthostatic hypertension associated with nephroptosis but strongly emphasized the fact that not all cases of nephroptosis are accompanied by hypertension. Only one patient, a female 56 years of age, who had been treated for benign hypertension for years and had entered a malignant phase of the disease, was subjected to operation after urologic study revealed a bilateral nephroptosis with a moderate right hydronephrosis. At operation a sclerotic aberrant vessel leading to the upper pole of the right kidney was ligated and a nephropexy was performed. Following the operation, the blood pressure remained elevated (above 200 mm.), but the episodes of cardiac, cerebral, and ocular symptoms disappeared and there was a marked symptomatic improvement. The authors urged that all hypertensive patients should be studied for the effect of posture upon the blood pressure and that those patients exhibiting orthostatic hypertension should receive pyelographic study and appropriate treatment, surgical or otherwise, if nephroptosis is disclosed.

I have observed 2 cases of hypertension associated with nephroptosis which are not included in Table I or II. The first patient was a female 19 years of age with a preoperative hypertension of 150/84, and following denervation of the renal pedicle and a Kelly nephropexy, the blood pressure fell to 130/80. The second patient was a female, 46 years of age, who had a preoperative hypertension of 156/86, and following pyelolithotomy and nephropexy, the blood pressure fell to 120/80 during her hospitalization. Unfortunately, a follow-up study of the blood pressure in both cases was not possible, as the patients left the city and could not be traced.

Ritch had previously reported excellent results from the standpoint of improvement in renal function and reduction in blood pressure which were achieved by establishing good urinary drainage by ureteral dilatation in a case of hydronephrosis with ptosis and obstruction at the ureteropelvic junction and by nephropexy in another case. Schroeder and Steele observed 2 cases of unilateral hydronephrosis associated with ptosis in their series of 71 cases of essential hypertension. Schroeder and Fish have described 2 cases of hydronephrosis with arterial hypertension treated by nephrectomy. An excellent result was obtained in their Case 6, in which a marked left hydronephrosis and hydroureter due to a stricture of the ureterovesical junction was removed despite the presence of a slight hydronephrosis and ptosis of the left kidney. Slight improvement manifested by a considerable reduction in blood pressure for six months was obtained in the patient in their Case 3, who had a nephrectomy for an advanced left hydronephrosis and a moderate hydronephrosis with ptosis on the right side.

(To be concluded in the July issue. The references will accompany the last section.)

Review of Recent Meetings

REPORT OF THE MEETING OF THE PACIFIC COAST SURGICAL ASSOCIATION, LOS ANGELES, CALIF., FEB. 19-22, 1941

H. H. Searls, M.D., San Francisco, Calif.

President's Address: The Surgical Aspects of Chronic Duodenal Ulcer, Charles T. Sturgeon, Los Angeles.—Sturgeon outlined the indications for surgical treatment and the different operative procedures in use. He recommended partial gastrectomy with partial duodenectomy as the operation of choice when the age and physical condition of the patient permit. He concluded with a warning that all patients should be kept under medical supervision for a long time after operation. An extensive list of references was appended.

A Family With Hemolytic Icterus, H. H. Searls, San Francisco.—Searls described a family in which four patients with congenital hemolytic icterus were encountered, from three of whom he had removed the spleen. He discussed the literature and presented the clinical picture of the disease. Case reports were included.

The paper was discussed by **J. H. Woolsey,** Woodland, Calif., who had observed that pregnancy in the presence of this disease was dangerous and had terminated fatally in several instances. He suggested that the surgical demonstration of deeply pigmented gallstones should suggest a study of the blood picture of the patient in order to rule out the possibility of hemolytic icterus. **H. Glenn Bell,** San Francisco, discussed the paper and reported a family of five persons who had the disease.

Back Disabilities Due to Strain of the Multifidus Muscle—Treated by Novocain Injections, William K. Livingston, Portland, Ore.—Livingston noted that in some cases of low back disability the essential lesion may be small and local, while the syndrome of widespread muscle spasm, neuritis, and so forth may result from secondary reflex disturbances. He pointed out that a very common location of such local lesions is the multifidus muscle in the region of the sacrum. If the "trigger point" can be located, novocain solution injected at this point may relieve the whole vicious cycle of reflexes.

Edgar L. Gilcreest, San Francisco, in discussion, observed that the cause of low back pain is often difficult to find. Stretching and manipulation gave relief in a large percentage of his cases, but he expressed gratitude that Livingston offered a new therapeutic measure for the treatment of this syndrome. **E. W. Rockey,** Portland, testified that Livingston had relieved him of a very serious pain in the back, which had followed a fall. **A. R. Kilgore,** San Francisco, reported a similar case. **Frederick Reichert,** San Francisco, emphasized the importance of accurately locating trigger points. **LeRoy Abbott,** San Francisco, reported having seen Lawrence Mayers, of Chicago, relieve pain by injection along

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the spine with a special solution which he calls "astroform." **Homer Dudley,** Seattle, Wash., warned that the pain may recur after such treatment.

Injuries to Ligaments of the Knee, LeRoy C. Abbott, John Saunders, and **Carl Anderson,** San Francisco.—In this article the authors stressed the importance of early and thorough examination of all injuries to the knee in order to establish promptly an accurate anatomic diagnosis and thereby apply the appropriate method of treatment. They described certain methods of examination of great practical value in arriving at the correct diagnosis and discussed the mechanism of injury to the ligament and the clinical findings in each type of injury. An outline of treatment concluded the paper.

Harold Hitchcock, Oakland, Calif., in discussion urged, for minor injuries, early strapping and exercises for the quadriceps. He pointed out that immobilization results in such a weakening of the quadriceps that the disability is considerably aggravated. Aspiration of the joint is an important part of the treatment. In the more serious injuries of the knee, examination should be done under anesthesia. **John C. Wilson,** Los Angeles, considered the authors' physiological and anatomical discussions of the knee joint to be of great practical value. In closing, **Abbott** again emphasized that early operation is of very great importance in severely damaged joints which show marked rocking and spread of the joint, by x-ray examination.

The Urological Complications of Carcinoma of the Rectum, Thomas F. Mullen and **Paul Lestrohan,** San Francisco.—The authors observed that symptoms related to the urinary tract are found in a high percentage of patients having cancer of the rectum and urged more specific attention to these symptoms before operation. They questioned the advisability of the routine use of the retention catheter and expressed the belief that if it is used it should always be accompanied by tidal irrigation. They recommended preservation of the pelvic splanchnic distribution to the urinary and sexual apparatus, whenever possible, by special attention to the anatomy of the posterior pelvic fascial planes. An effort should be made to prevent prolapse of the bladder into the posterior wound, and every attention given to the prevention of postoperative cystitis.

Frank Hinman, San Francisco, discussed this paper, concluding that these patients should have a complete urological study before operation, anatomical dissection at operation, and that the problem of urological complications should have careful attention both before and after operation. **E. Eric Larson,** Los Angeles, recommended the use of chemotherapy as a prophylactic preoperative measure for the prevention of urinary infection and urged that the surgeon obtain the co-operation of a competent urologist before, during, and after operation.

Acute Pancreatitis, George K. Rhodes, San Francisco.—Rhodes discussed the etiology, clinical picture, and differential diagnosis of this disease. The blood amylase determination was considered to be of great aid in differential diagnosis. He recommended conservative treatment during the acute stage whenever possible.

E. Eric Larson, Los Angeles, in discussion, described the serum amylase test and again emphasized its value as an aid to the diagnosis of acute pancreatitis. **H. Glenn Bell,** San Francisco, warned that, as a general policy, too much weight should not be placed on a laboratory procedure and that there was a possibility of missing other acute conditions in the abdomen by not operating.

The Problem of the Common Duct Stone, J. H. Woolsey, Woodland, Calif.—Woolsey discussed the etiology and diagnosis and emphasized the value of variations in the icterus index at the time of colic, the rise going from 8 to 16 and even to 33 per cent. In all of his cases in which this variation was noted, stones

were present in the common duct. He then discussed the treatment and urged that, in doubtful cases, exploration should be done.

Wayland A. Morrison, Los Angeles, in discussing Woolsey's paper, said that he was in agreement with Woolsey in urging more frequent exploration of the common duct. **George K. Rhodes,** San Francisco, recommended the use of vitamin K in jaundiced patients and the making of cholangiograms at the table. He emphasized the importance of using considerable carbohydrate infusion before operation.

Secondary Operations on the Biliary System After Cholecystectomy, Robert D. Forbes, Seattle.—The author discussed the hazards of the approach in operating for the second time. He named the indications for this operation (the most common being some form of obstructive jaundice) and then discussed the differential diagnosis, finally reviewing a series of records of fifteen patients upon whom operations had been performed for biliary disease following cholecystectomy. The author urged a more frequent exploration of the common duct at the time of performing cholecystectomy.

Verne C. Hunt, Los Angeles, said that, in his opinion, the common duct should be opened much more frequently than is the present practice in performing cholecystectomy. He felt that this would be an important prophylactic move against the development of the type of cases described by Forbes.

Aseptic Technic for Resection of the Stomach, Emile F. Holman, San Francisco.—Holman presented a motion picture in illustration of this subject. By using Payr clamps and a cautery, he was able to do a partial gastrectomy under aseptic conditions, no viscus being opened at any time. There was no discussion.

An Instrument for Retraction of Viscera During Peritoneoscopy, Samuel Robinson and **L. Gordon Fiske,** Santa Barbara, Calif.—The authors described an instrument which, at the time of peritoneoscopy, may be inserted through a separate puncture wound into the abdomen. It consists of a cannula or tube, through which a web-footed retractor is inserted into the abdomen. The web foot consists of three blades which open fanwise when a thread is turned at the proximal end of the shaft. These three blades are covered with a latex seamless rubber bag, shaped like a tennis racket. The neck of the bag is tied to the shaft of the retractor with silk thread. Under the observation of the peritoneoscopist, looking through his peritoneoscope, the retractor is used to move about the different viscerae to give a better view of what is being seen.

John C. Ruddock, Los Angeles, who has had a very extensive experience with peritoneoscopy, stated in discussion that he would welcome this instrument as an adjunct to his work. He then went on to classify the work of the peritoneoscope as to what it would show, the type of patient to be selected for its use, and so forth. **Harold Brunn,** San Francisco, although admitting the value of the peritoneoscope, pointed out that errors of interpretation made in using it might be extremely dangerous or even fatal.

Hyperparathyroidism, H. S. Chapman, Stockton, Calif.—After a complete discussion of the literature and a careful clinical description of the disease, the author presented his own case.

P. K. Gilman, San Francisco, in discussion, reported two cases from the Stanford Hospital. **H. H. Searls,** San Francisco, discussed the laboratory findings, anatomy, and operative procedures in these cases.

New Treatment for Residual and Progressive Postoperative Exophthalmos, Brien King, Seattle.—King presented a preliminary report in which he stated that x-ray therapy to the general region of the front of the neck had resulted in the

regression of postoperative exophthalmos. Admitting the method to be empirical, he nevertheless hoped that others would follow his lead so that a sufficient number of cases could be observed to assay its value.

Howard C. Naffziger, San Francisco, in discussion hoped that accurate observations with the exophthalmometer would be performed and that many basal metabolic rates would be determined in the further investigation of this method of treatment.

Carcinoma of the Cervical Stump, Raymond E. Watkins, Portland.—Careful preoperative study of patients requiring hysterectomy for seemingly benign conditions would reveal associated carcinoma in most instances when cancer is associated. The prognosis in true carcinoma of the stump is much brighter than is generally recognized. Irradiation of cervical stump cancer is the method of choice. The author performs total hysterectomy for benign tumors if the patient has a diseased cervix, because he feels that cervical lacerations, endocervicitis, cystic degeneration, and extensive erosion are definitely predisposing factors in the production of carcinoma. If total hysterectomy is contraindicated because of the condition of the patient, the cervix can be treated from below at a later time. He believes that leaving the normal cervix subjects the patient to little risk. Removal of the endocervical mucous membrane is of limited value. A careful preliminary study of every patient who is to be subjected to hysterectomy should be done.

A. R. Kilgore, San Francisco, in discussing this paper, recommended subtotal hysterectomy in young women with a healthy cervix, but in older women in the cancer age, and particularly in those whose cervices are diseased, total hysterectomy should be performed.

An Appliance for Colostomy Control, O. F. Lamson, Seattle.—The author demonstrated a mechanism he devised for the control of a colostomy. A small, thin-walled rubber bag could be inflated after being placed within the colostomy and attached by a hollow tube to a plastic disk which rested on the external opening. The thickness of the abdominal wall was first measured in order to have the proper length of tubing. This tubing serves the purpose of holding the bag to the disk on the abdominal wall and also permits the passage of air into the bag when it is being inflated. The author stated that it had been used successfully in a number of cases. A general discussion indicated that the members of the Association felt that this apparatus might have a distinct place in the control of a colostomy.

Book Reviews

The Endocrine Function of Iodine. By William T. Salter. Cambridge, 1940. Harvard University Press. Pp. 351, with 38 illustrations.

This monograph brings together between covers for the first time a comprehensive account of the chemical, physiologic, and clinical information relating to the metabolism and function of iodine compounds in the animal body. It is written from the background of extensive experimental experience in the field and is of unquestionable value to anyone interested in thyroid function in health or disease. The author has reviewed the older as well as the most recent literature, covering 588 references, and has adequately described the results of studies of iodine balance, of tracer experiments with radio iodine, of estimations of circulating iodine in health and disease, and of other observations. The style is lucid and readable.

A Method of Anatomy. Descriptive and Deductive. By J. C. Boileau Grant, M.C., M.B., Ch.B., F.R.C.S. (Edin.). Professor of Anatomy in the University of Toronto. Ed. 2, Baltimore, 1940, The Williams and Wilkins Co. $6.

Medical knowledge is increasing much more rapidly than is the power of the human mind to learn and retain the vast amount of scientific facts before us. Anatomy, pathology, physiology, and therapeutics only a few years ago were the mainstays of the study of medicine, but now the new discoveries in biochemistry, chemotherapy, and the extreme development of specialties make it necessary that the time spent on the old fundamentals be shortened that the new essential information be taught. This necessitates short cuts by new methods of teaching and study of anatomy since the student of today now has one-fourth to one-third the number of hours to devote to this subject as compared to students of twenty to thirty years ago. It is with considerable misgiving that we accept this new order, though we realize the necessity of the change. *A Method of Anatomy* is an experiment in teaching anatomy by a short method which should be given a trial. One cannot believe it possible for one to acquire extensive anatomical knowledge without more time and the older methods of systematic dissection. Still a good working knowledge of the subject should result from a study of this book and we wait with interest the results of its more extensive use in medical schools. The coordinate presentation of physical facts and functions of the anatomical parts with simple illustrations is impressive and should help the student to retain his anatomy.

The second edition of this unique book differs from the first in the addition of a section on general anatomy and the insertion of more than 100 new figures. The new figures are line drawings of excellent quality depicting actual dissections with great clarity and accuracy. Most of them are of half-page size and completely labeled. The section on general anatomy covers many of the more important facts of systematic anatomy with telegraphic briefness but is nevertheless very readable

and enlivened by considerable practical physiology. The brain, and the endocrine glands as a system are not considered. These are regrettable omissions since their addition would furnish the beginning student with an excellent sketch of the entire scope of his anatomical training. Numerous minor improvements have been made throughout the original text, but with the exceptions noted above, the second edition differs little from the first. Missing is a list of references that would enable the reader to locate the work of the numerous authors mentioned throughout the book. Professor Grant's book remains what the title suggests, a method of presenting gross anatomy to the beginning student. As such it offers a distinct and admirable challenge to teachers of anatomy to present their subject in an equally lucid manner and to the student a refreshing relief from dry bones and lifeless muscles; however, it does not eliminate the need for each medical student to possess one of the larger standard textbooks of anatomy, both for his anatomical courses and as a reference in subsequent years. Other than a book for medical students we believe it will be of good value for the graduate who wishes to review his anatomy. He will find the subject presented in a manner that will make anatomical study a pleasure.

The Injured Back and Its Treatment. Edited by John D. Ellis, M.D. Cloth. Pp. 377, Springfield, Ill., 1940, Charles C Thomas, Publisher. $5.50.

This timely book of convenient size is beautifully printed and well illustrated. It is alone in its field and it presents a compilation of present-day information which should make it a useful addition to the libraries of all practitioners who are called upon to diagnose and treat painful backs. The contents are divided into nine chapters, of which three are by the editor and the remaining six by seven contributing authors. Ellis presents a most valuable chapter of sixty pages on "The Routine Examination of the Injured Back," giving a clear discussion and differentiation of the injuries of the lower back and related conditions. Professor Sir Arthur Keith has written the introductory chapter and discusses the posture of man from the viewpoint of comparative anatomy and physiology. Conwell presents compression fractures of vertebral bodies and Davis and Haven discuss neurosurgic aspects of back injuries. Ghormley discusses the diagnosis and treatment of conditions involving the articular facets and Osgood gives us an inspiring chapter on faulty body mechanics and posture in relation to both the prevention and care of back injuries. A very valuable and instructive chapter has been contributed by Davis on backache as a symptom of visceral disease and reflex pains in the back which may be mistakenly considered as due to injury. This chapter should be valuable to those who are called upon to treat or testify where objective symptoms are absent and the injury is questionable.

A chapter presenting modern methods of first aid and transportation of injured backs would have been welcome, and it is to be hoped that the present-day standardized procedures will appear in the next edition. There is considerable valuable information on x-ray diagnostic procedures distributed through the book, but it is inadequately indexed and hard to find. A chapter in the next edition devoted to directions for the taking of diagnostic x-rays of the different parts of the spine would furnish a much needed addition, because this book will be useful in the more remote sections of the English-speaking world as well as in the large medical centers.

Clinical Pellagra. By Seale Harris, M.D., Professor Emeritus of Medicine, University of Alabama, and Seale Harris, Jr., M.D., Formerly Assistant Professor of Medicine, Vanderbilt University. Pp. 494, with 70 illustrations, including 4 in color. St. Louis, 1941, the C. V. Mosby Company. $7.

In view of the striking and rapid advances in the field of nutritional diseases, Seale Harris' *Clinical Pellagra* is especially welcome to the clinician.

Written in admirable, conversational style, the book is replete with the salient features and cogent factual information of students of pellagra the world over; in addition, one derives benefit from the mature, keen analysis and interpretations of a number of leading experts in the field of nutrition. Among the many salient features of the book are included a fascinating and extraordinarily complete history of the disease, an interpretation of the available theories of the etiology of pellagra in the light of modern investigative advances, special sections by Ruffin, Smith, Sydenstricker, Porter, Higginbotham, and others, dealing with special problems in pellagra, lending immensely to the value of the text. The rationale of the treatment of the pellagrous patient is so clearly indicated that the veriest tyro in the field of nutritional problems may easily master the fundamental principles of the management of pellagra.

The book consists of six sections, dealing with the history of pellagra, its etiology, current clinical investigations, symptomatology, diagnosis and prognosis, prophylaxis, and treatment. Numerous excellent plates illustrate the clinical manifestations of the disease. An extensive bibliography includes virtually every significant contribution to the study of pellagra. Certainly the book constitutes the most concise, well-authenticated treatise on pellagra extant today.

Dr. Harris has succeeded in writing "a factual treatise on pellagra, in which the various phases of the subject are discussed, including summaries of the most important contributions by those who may be regarded as authorities on the subject."

Endocrine Gynecology. By E. C. Hamblen. Cloth. Pp. 453, with 169 illustrations. Springfield, Ill., Charles C Thomas, Publisher. $5.50.

The author has done a magnificent task with a subject that is changing rapidly as a result of the relatively enormous amount of investigative work that is being done in the field of gynecologic endocrinology. The style is easy, and the clearly written text is profusely illustrated. The color plates have been beautifully prepared, and the photomicrographs are good, being adequate to complete the descriptions of each disease considered.

One of the outstanding qualities of the book is the clear thinking along lines of histopathologic diagnosis with a resultant logical course in treatment. The terminology is accurate, and such conditions as menstruation and anovulatory bleeding are definitely catalogued, with vague terms as functional bleeding avoided. The psychic influence on the behavior of the glands of internal secretion has never before been as clearly described nor emphasized as much.

Though the author admittedly has written this text for the physician doing general practice, the subject is thoroughly covered and the references are complete, making the book suitable for many other physicians, especially those doing gynecology.